TO EVALUATE ADD ON EFFECT OF HYDROXYETHYL STARCH WITH LIGNOCAINE FOR PAIN RELIEF FOLLOWING PROPOFOL ADMINISTRATION

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Dedicated

to

My Family &

My Teachers

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DR. BHAWYA CHUGH

LIST OF ABBREVIATIONS

ASA - American Society of Anesthesiologists

BMI-BODY MASS INDEX

CNS-CENTRAL NERVOUS SYSTEM

DBP- DIASTOLIC BLOOD PRESSURE

EDTA- ETHYLENE DIAMINE TETRA ACETIC ACID

GABA - GAMMA-AMINOBUTYRIC ACID

HES-HYDROXYETHYL STARCH

HR- Heart Rate

5HT3- 5-HYDROXYTRYPTAMINE 3

i.e.- id est /That is

IV- Intravenous

kg- KILOGRAM

mcg- MICROGRAM

MCT-MEDIUM CHAIN TRIGLYCERIDES

mg- MILLIGRAM

mins- MINUTES

NIBP-NON INVASIVE BLOOD PRESSURE

N_2O- NITROUS OXIDE

NRS- Numerical Rating Scale

NSAIDS- NON STEROIDAL ANTI INFLAMMATORY DRUGS

NYHA- NEW YORK HEART ASSOCIATION

SBP- SYSTOLIC BLOOD PRESSURE

secs- SECONDS

SpO2- SATURATION OF PERIPHERAL OXYGEN

TRPA1-TRANSIENT RECEPTOR POTENTIAL ANKYRIN 1

TRP-TRANSIENT RECEPTOR POTENTIAL

TRPV-TRANSIENT RECEPTOR POTENTIAL VANILLOID

vs- Versus

yrs- YEARS

ABSTRACT

Introduction: Propofol is the most widely used Intravenous (IV) induction agent in anaesthesia. Pain on injection with propofol is a common problem and can be very distressing to the patient. Even with multi-modal techniques, pain on propofol injection is not abolished completely.
HydroxyEthyl Starch (HES), a colloid, is a clinically safe and well tolerated complex polysaccharide and has the capacity to modify endothelial cell junctions and permeability of the vascular endothelium. Pre administration of HES may prevent contact activation by propofol, which may in turn lead to reduced pain during propofol injection.
Aim of Study: To compare the incidence and severity of pain on propofol injection in patients pre administered with 6% HES with 2% lignocaine or 0.9% saline with 2% lignocaine during induction of anaesthesia.
Materials & methods: A prospective randomized study was conducted on 206 ASA (American Society of Anesthesiologists) I and II patients of age 18-65 years (yrs) undergoing elective surgery under general anaesthesia who were randomly allocated into Group 'H' and Group 'S' of 103 patients each. Patients in Group 'H' were administered 50 ml of 6% HES with 2% lignocaine [1milligram/kilogram (mg/kg)] while patients in Group 'S' were administered equal volume of 0.9% Saline with 2% lignocaine (1mg/kg) two minutes (mins) before induction with 1% propofol (2mg/kg). The incidence and severity of pain on propofol injection was calculated using Numerical Pain Rating Scale (NRS) every 15 seconds (secs) till the loss of verbal command.
Results: The incidence of pain was significantly reduced in Group H at 15, 30, 45, 60 seconds (35%, 49.5%, 57.3%, 15.5% respectively) compared to Group S (83.5%, 97.1%, 96.1%, 27.2% respectively) with p value being 0.001.

The NRS score was also significantly reduced in Group H at 15, 30, 45, 60 seconds (0.39 ± 0.58, 0.72 ± 0.91, 0.91 ± 0.94, 0.59 ± 0.67 respectively) compared to Group S (2.12 ± 1.46, 3.23 ± 1.25, 3.53 ± 1.27, 3.57 ± 1.20 respectively) (p value 0.001).
At 15 seconds after starting propofol infusion, Group S had a higher incidence of mild pain compared to Group H [63.1% versus (vs) 35%], and Group S also experienced more moderate pain than Group H (20.4% vs 0%). By 30 seconds, Group S still had a higher incidence of mild pain than Group H (58.3% vs 48.5%), and Group S continued to experience more moderate pain than Group H (38.8% vs 1%). At 45 seconds, Group S showed a higher incidence of moderate pain compared to Group H (48.5% vs 1%), while Group H had more mild pain than Group S (56.3% vs 47.6%). By 60 seconds, Group S had a higher incidence of moderate pain compared to Group H (16.5% vs 0%), whereas Group H had more mild pain than Group S (15.5% vs 10.7%). These differences in pain severity between the two groups were statistically significant. No patients in either group experienced severe pain at any time point.
Conclusion: The combination of IV 6% HES with 2% lignocaine is superior to using 0.9% saline with 2% lignocaine in alleviating pain after propofol injection.

Keywords: Propofol, Hydroxyethyl starch, 2% Lignocaine, 0.9% Saline, Numerical Rating Scale

TABLE OF CONTENTS

S.NO.	TOPIC	PAGES
I	INTRODUCTION	1-6
II	AIMS AND OBJECTIVES	7
III	REVIEW OF LITERATURE	8-30
IV	MATERIALS AND METHODS	31-35
V	OBSERVATIONS AND RESULTS	36-54
VI	DISCUSSION	55-60
VII	SUMMARY AND CONCLUSIONS	61-62
VIII	BIBLIOGRAPHY	63-70

APPENDICES–I

- PROFORMA
- MASTER CHART

APPENDICES–II

- APPROVAL LETTER OF THESIS PLAN
- THESIS PLAN

LIST OF TABLES

TABLE NO.	TITLE	PAGE NO.
1a	Distribution according to Age, Weight and BMI	37
1b	Distribution of subjects according to Gender	37
1c	ASA Physical Status	37
2	Haemodynamic Parameters	41
3a	Incidence of pain before giving Study Drug	42
3b	Incidence of pain 15 secs after starting propofol infusion-	43
3c	Incidence of pain 30 secs after starting propofol infusion	44
3d	Incidence of pain 45 secs after starting propofol infusion	45
3e	Incidence of pain 60 secs after starting propofol infusion-	46
4	NRS for pain at cannula site	47
5a	Severity of pain at cannula site before administering study drug	49
5b	Severity of pain 15 secs after starting propofol infusion	50
5c	Severity of pain 30 secs after starting propofol infusion	51
5d	Severity of pain 45 secs after starting propofol infusion	52
5e	Severity of pain 60 secs after starting propofol infusion	53
6	Mean Propofol duration (secs)	54

LIST OF FIGURES

FIGURE NO.	TITLE	PAGE NO.
1	Structure of propofol	8
2	Structure of hydroxyethyl starch	28
3	CONSORT flow diagram of the study	36
4	Mean Age Distribution	38
5	Gender	39
6	Mean Weight	39
7	Mean Body Mass Index (BMI)	40
8	ASA Physical Status	40
9	Incidence of Pain before administering study drug	42
10	Incidence of Pain 15 secs after starting Propofol infusion	43
11	Incidence of Pain 30 secs after starting Propofol infusion	44
12	Incidence of Pain 45 secs after starting Propofol infusion	45
13	Incidence of Pain 60 secs after starting Propofol infusion	46
14	NRS for pain at cannula site	48
15	Severity of Pain before administering study drug	49
16	Severity of pain 15 secs after starting propofol infusion	50
17	Severity of pain 30 secs after starting propofol infusion	51
18	Severity of pain 45 secs after starting propofol infusion	52
19	Severity of pain 60 secs after starting propofol infusion	53
20	Mean duration of Propofol administration	54

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INTRODUCTION

IV induction is the most commonly used method for induction of general anesthesia. An optimal choice for IV anaesthetic agent should provide the triad of anaesthesia which include hypnosis, amnesia and analgesia, while being free of undesirable cardiac and respiratory side effects. Commonly used IV anaesthetics are barbiturates such as thiopentone and non barbiturates such as propofol, etomidate, ketamine.[1]

Propofol ranks as one of the most commonly utilized IV anaesthetic agent for both induction and maintenance of anaesthesia. It is a basic phenol with two adjacent isopropyl groups next to the hydroxyl group (ortho positions).[2] The currently most available formulation is 1% weight/ volume (w/v) aqueous emulsion containing 10% w/v soya bean oil as a solubilising agent, with 1.2% w/v egg phosphatide used for emulsifying and 2.25% w/v glycerol for ensuring isotonicity, sealed under cover of nitrogen. Its pH ranges from 6 to 8.5 and pKa is 11 in water. Propofol should be stored a temperature below 25°C to prevent degradation.[3] Ethylene-diamine-tetraacetic acid (EDTA) or sodium metabisulfite is added as a preservative.

Propofol exhibits several desirable properties, including rapid onset, short duration of action (5-10 mins), ease of titration, minimal post operative nausea and vomiting, greater depression of laryngeal reflexes compared with other anaesthetic agents and minimal side effects making it an ideal IV anaesthetic agent.[1] However, despite propofol fulfilling all criteria of being a near ideal anaesthetic, the pain associated with propofol injection remains an important issue. There have been many instances where patients recalled the experience of induction of anaesthesia as the most uncomfortable aspect of the peri-operative phase. The incidence of propofol injection pain varies widely among adults (28% to 90%) [4, 5] and children (28% to 85%) [6, 7] with younger patients experiencing higher incidence and severity of propofol injection pain.[8]

As a result, numerous interventions have been researched to mitigate the discomfort caused by propofol injection.

Pain upon propofol injection can occur immediately or with a delay. Immediate pain likely arises from a direct irritant effect, while delayed pain, occurring with a latency period of 10 – 20 secs is probably due to an indirect effect through kinin cascade.[3, 9] Propofol emulsion can activate the kallikrein-kinin system upon contact with vein nerve endings. Activation of factor XII converts prekallikrein to kallikrein. Kallikrein cleaves high-molecular weight kininogen to release bradykinin. Bradykinin causes vasodilatation and increases permeability of vein, which in turn increases contact between aqueous phase of propofol and free nerve endings of vein, resulting in pain.[10, 11]

The cause of pain on propofol injection is not well understood so far. There are many factors which seem to play a role in causation of pain. These factors encompass the injection site, vein size, injection rate, concentration of propofol in the aqueous phase and blood buffering capacity.[3] Additional crucial considerations involve the rate of IV carrier fluid, propofol temperature, syringe material and the concurrent administration of drugs like opioids and local anaesthetics.[3] Activation of nociceptive receptors like 5-HT3 (5-Hydroxy Tryptamine 3) receptors,[12] human transient receptor potential ankyrin 1 (TRPA1][13] as well as irritation of the venular endothelium by the phenol moiety of propofol have also been related to propofol injection pain.[14] The sensation of pain from veins likely originates from neural elements located within the wall of veins, likely from free afferent nerve endings located between the media and intima. The pain-conducting axons are part of the myelinated A delta group.[15]

According to Scott et al, the size of the vein plays a crucial role. They observed that injecting propofol into a larger vein in the antecubital fossa resulted in no pain. This is likely because the drug was injected into the midstream of blood flow within the vein's lumen; minimizing contact with the sensitive vein wall at high concentrations.[16] Another factor influencing pain is the duration of exposure of the vein wall to propofol. Slow injections of propofol are more painful than rapid

boluses, possibly because the rapid bolus clears quickly from the vein and is swiftly replaced by blood flow. Pain severity correlates with higher concentrations of propofol. At a given concentration, pain is consistently greater when propofol is mixed with glucose compared to intralipid as the diluent.[17] This discrepancy may stem from the reduced concentration of propofol in the aqueous phase. In propofol emulsions, the drug is distributed differently between the outer aqueous phase and the inner lipid phase. During a bolus injection, only the outer aqueous phase contacts the vein's intima. The concentration of an irritant agent in the aqueous phase could potentially cause venous pain upon injection.[18]

Huang et al proposed that when the infusion rate of the carrier IV fluid is slow, fewer kininogen molecules may be generated due to the limited contact area between propofol and the vein endothelium, which results from the smaller volume of IV fluid administered. Moreover, propofol may be buffered by the dilution effect of venous blood. Conversely, with a fast infusion rate of the carrier IV fluid, the dilution effect of venous blood diminishes due to the large volume of IV fluid administered, leading to propofol being primarily diluted by the aqueous solution. Consequently, the pain intensity associated with propofol increases due to the higher concentration of propofol in the aqueous phase.[19]

McCrirrick and Hunter investigated the impact of injectate temperature on propofol injection pain. They observed a significant reduction in injection pain incidence when propofol was administered at 4°C. They theorized that the lower temperature might slow down the kinin cascade.[20] Similarly, Fletcher and colleagues discovered that heating propofol to 37°C decreased the incidence of injection pain from 59% to 22%. This effect could be attributed to temperature influencing mediator release and the partition coefficient, thereby affecting the concentration of propofol in the aqueous phase.[21]

Several approaches to minimize pain from propofol injection include administering it in larger veins, combining it with lignocaine beforehand, pre-administering opioids, using sub-anaesthetic doses of ketamine,

and employing a carrier emulsion containing a mixture of medium and long chain triglycerides.[14, 22]

The use of lignocaine to prevent pain from propofol injection is extensively researched and widely employed in clinical settings. Lignocaine can be used either as a pre-treatment before propofol administration or mixed directly with propofol to mitigate injection discomfort. Administering lignocaine before propofol injection reduces pain by potentially exerting a local anaesthetic effect on the vein.[3] Additionally, when lignocaine is mixed with propofol, it lowers the pH of the mixture, thereby decreasing the concentration of propofol in the aqueous phase and consequently reducing the pain associated with propofol injection. [23]

Furthermore, lignocaine may potentially stabilize the kinin cascade, as suggested by Scott et al .[16] Although lidocaine is frequently combined with propofol to mitigate injection pain, the mixing of propofol with any other drug is generally not recommended. However, the addition of lidocaine to propofol can lead to the aggregation of oil droplets, posing a risk of pulmonary embolism.[24] Reddy and colleagues mixed 20mg of 2% lignocaine with 9 ml of 1% propofol to alleviate injection discomfort. After 90 minutes, they observed that propofol had separated into distinct layers within the syringe. Their findings indicate that the stability of the propofol-lignocaine emulsion may be compromised, particularly with higher doses of lignocaine or prolonged storage between preparation and administration.[25]

Other agents employed to mitigate pain include ketamine, thiopentone, procaine, opioids, and antiemetics such as metoclopramide, ondansetron and dexamethasone. Combining two or more of these drugs or approaches significantly reduces the incidence of pain caused by propofol injection. Therefore, a multimodal approach is recommended to effectively minimize propofol injection-induced pain. However, even with multimodal techniques, complete abolition of pain from propofol injection may not always be achieved.

HES is a synthetic, colloidal structured polymer derived from amylopectin. It consists of a group of polydisperse colloid solutions

composed of large, ethylated, polymerized amylopectin molecules. The various formulations within the HES family differ significantly in their physicochemical properties, pharmacokinetics, composition, and potential adverse effects. Classified pharmacologically as a plasma expander, HES is designed to support oncotic pressure and maintain electrolyte balance.[26] It possesses the ability to modulate endothelial cell junctions, affect vascular endothelial permeability, and inhibit endothelial activation triggered by various substances and molecules, including propofol. Additionally, its uptake by reticuloendothelial cells may influence inflammatory responses.[27, 28] Experimental models both in vivo and in vitro have demonstrated the capacity of starches like HES to modify endothelial cell junctions and potentially impact inflammatory processes. Therefore, pre-administration of HES might mitigate contact activation by propofol, thereby potentially reducing pain associated with propofol injection.

Prasad in 2018 did a study to investigate how pre-administering 6% HES affects pain reduction during propofol injection. The study found that pre-administering 100ml of 6% HES 130/0.4 three to five mins before propofol injection significantly reduces the discomfort compared to injecting with normal saline.[29]

Misra et al also studied the impact of pre-administering 6% HES on injection pain using a 3-point Likert Scale following induction of anaesthesia with a premixed solution of 1% propofol and 2% lidocaine. They observed a significant reduction in pain upon propofol injection, which they attributed to the endothelial modulation facilitated by HES administration.[30]

Therefore, we hypothesized that employing a multimodal approach involving the concurrent administration of 6% HES and 2% lignocaine would more effectively alleviate pain during propofol injection. Additionally, utilizing a NRS would provide greater objectivity in assessing pain intensity. Consequently, we aimed to compare the incidence and severity of propofol injection pain after pre-administration of 6% HES with 2% lignocaine versus pre-administration of 0.9% saline

with 2% lignocaine in patients undergoing anaesthesia induction with 1% propofol.

AIMS AND OBJECTIVES

- To compare the incidence of pain on propofol injection in patients receiving 6% HES with 2% Lignocaine versus 0.9% Saline with 2% lignocaine.
- To compare the severity of pain on propofol injection in the two groups.

REVIEW OF LITERATURE

The discovery of anaesthesia has revolutionized the practice of modern medicine. Modern anaesthesia can be achieved through various ways, with IV anaesthesia being the most commonly used technique. There are four drugs known for inducing IV anaesthesia: propofol, thiopentone, etomidate and ketamine. Among these, propofol stands out as an ideal IV anaesthetic agent due to its rapid return of consciousness and minimum central nervous system (CNS) side effects. It is widely used for both inducing and maintaining anaesthesia.

Propofol, originally developed in United Kingdom by Imperial Chemical industries as ICI 35868, was first introduced in 1977. Initially formulated with a solution named as Cremaphor EL, it was later withdrawn because of anaphylactic reactions.[31]

Propofol is chemically a substituted isopropyl phenol, scientifically known as 2, 6 - diisopropyl phenol.

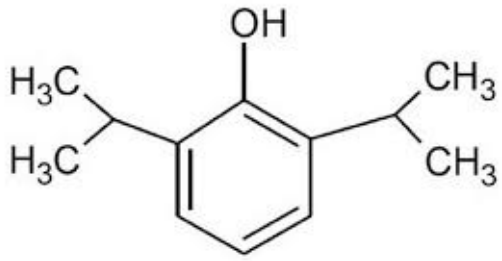


Figure 1: Structure of propofol

There are several formulations of propofol currently available. The most widely used composition includes 1% propofol containing 10% soybean oil, 1.2% purified egg phospholipid, and 2.25% glycerol. Additionally, EDTA or sodium metabisulfite is included for their bacteriostatic properties.

Propofol acts as a global CNS depressant by directly activating Gamma - aminobutyric acid (GABA- A) receptors. It also enhances activity at glycine receptors, contributing to propofol induced hypnosis.[32] Propofol also inhibits the N-methyl-D-aspartate receptor and modulates influx of calcium through slow Calcium channels. It exhibits a quick onset of action along with a dose-dependent hypnotic

effect and allows for swift recovery even following extended usage. Additionally, propofol reduces cerebral oxygen consumption, lowers intracranial pressure, and possesses potent anticonvulsant properties.[33] Moreover, it acts as a potent antioxidant, displays anti-inflammatory properties, and acts as a bronchodilator. These attributes have contributed to an increased utilization of propofol in managing conditions such as traumatic brain injury, status epilepticus, status asthmaticus, delirium tremens, and critically ill patients with sepsis. Propofol is well known for its exceptional safety profile.

Complications associated with propofol use include hypotension, allergic complications, propofol infusion syndrome (especially with high dose infusions), hypertriglyceridemia and pancreatitis etc. Propofol also has abuse potential. The death of music pop star Michael Jackson in 2009 was from overdose of propofol as he was receiving it as a sleep aid.[34]

Propofol strongly supports micro bacteria growth. Many post operative surgical infections have been attributed to extrinsic contamination of propofol.[35] So strict asepsis should be maintained while handling propofol. Measures such as disinfecting the ampule neck with 70% isopropyl phenol and discarding the contents of an opened ampule within 6 hours if unused are recommended.[36] The most commonly reported adverse effect is pain upon injection.

Several factors influence the occurrence of pain upon propofol injection. These include the site of injection, vein size, injection speed, the concentration of propofol in the aqueous phase, and the buffering capacity of blood. Additionally,the rate of the IV carrier fluid, propofol temperature, syringe material, and concurrent use of drugs like opiates and local anaesthetics are significant factors contributing to pain associated with propofol injection. Pain from propofol injection can manifest immediately due to a direct irritant effect, while delayed pain, typically occurring with a latency of 10 to 20 secs, is thought to result from an indirect effect via the kinin cascade.[3, 9] Despite several proposed mechanisms, the precise reason of pain upon propofol injection remains incompletely understood.

Klement and Arndt in 1991 suggested that pain upon injection of certain anaesthetic agents is exacerbated by their non-physiological osmolality or pH. They observed that pain occurred at 1 osmol/kg during infusion and 3 osmol/kg during rapid injection. Acidic solutions with pH values below 4 and alkaline solutions with pH values above 11 also induced pain. They noted that pain latency decreased with higher osmolality, acidity, and alkalinity levels. These factors, combined with the volume injected and blood flow through the vein, influenced the degree of pain experienced. They additionally proposed that pain sensation originating from veins are likely due to neural elements within the vein walls, possibly stemming from free afferent nerve endings present between the media and intima. These pain-conducting axons are thought to belong to the myelinated A delta group. Pain associated with injection of diazepam and etomidate is attributed to the extreme osmolalities of their conventional formulations. This view is supported by the reduction of pain incidence to less than 1% with new formulations of these drugs that have osmolalities similar to that of blood.[37]

However, propofol has an almost isotonic, non-hyperosmolar formulation with a pH between 6 and 8.5. Therefore, Klement and Arndt's theory does not fully explain the pain caused by propofol injection.

Scott et al in 1988 identified several factors contributing to pain upon propofol injection. They emphasized the significance of vein size, noting that injecting propofol into a large vein in the antecubital fossa resulted in no pain. This is likely because the drug is introduced into the mainstream blood flow within the vein lumen, minimizing direct contact with the sensitive vein wall, especially at higher concentrations. Additionally, propofol may be effectively buffered by the freely mixing blood. Another crucial factor identified was the length of time the vein wall is exposed to propofol injection They observed that a slow injection of propofol caused more pain compared to a rapid bolus, suggesting that rapid clearance of the drug from the vein, replaced by blood, might contribute to reduced pain.

Scott et al also noted species variation in propofol injection pain and proposed that pain is more likely an indirect irritant effect due to the release of mediators rather than being a direct irritant effect. They explained that when the active components of the propofol emulsion contact the vascular endothelium, mediators such as kininogen are released from the kinin cascade, stimulating pain with a slightly delayed onset compared to direct effects. Furthermore, they found that the use of fat emulsion with propofol had minimal impact on the incidence of propofol injection pain. In summary, Scott et al.'s findings highlight vein size, injection speed, species differences, and the role of mediators released upon contact with the vascular endothelium as critical factors influencing pain upon propofol injection.[16]

Klement and Arndt in 1991 proposed that pain upon propofol injection correlates with the propofol concentration in the aqueous phase rather than the overall formulation, given that propofol has nearly physiological osmolality and pH (0.303 osmol/kg, pH 8.0). They demonstrated that pain intensity increased with higher concentrations of propofol and was consistently greater when glucose was used as the diluent compared to intralipid. Reducing the propofol concentration in the aqueous phase with intralipid effectively reduced injection pain.[17]

Doenicke et al in 1996 hypothesized that the concentration of propofol in the aqueous phase is a critical factor influencing pain related with its injection. In the preparation of propofol emulsion, the drug is distributed differently between the outer aqueous phase and the inner lipid phase. During a bolus injection, only the outer aqueous phase directly contacts the vein intima. They conducted a study comparing the addition of saline versus long-chain triglyceride fat emulsion to propofol and found consistent results supporting their hypothesis. They concluded that pain upon propofol injection is linked to the amount of propofol present in the aqueous phase of the emulsion and suggested that reducing this concentration can mitigate injection pain.[18]

Fischer et al conducted a study in 2010 exploring the effects of different propofol formulations on mouse and human transient TRPA1 channels. Their findings indicated that transient receptor potential

(TRP) channels, particularly TRP vanilloid 1 (TRPV1) and TRPA1, which are expressed in peripheral neurons responsible for detecting noxious stimuli such as thermal and chemical irritants, play a role in the sensation of pain induced by propofol. Activation of these TRP channels triggers the release of calcitonin gene-related peptide from both central and peripheral terminals of sensory neurons. This release leads to vascular leakage and dilation, contributing to neurogenic inflammation in peripheral tissues and central sensitization in the dorsal horn of the spinal cord. These mechanisms are implicated in the delayed pain sensation observed after propofol injection. In summary, Fischer's et al study suggested that activation of TRP channels, particularly TRPV1 and TRPA1, and subsequent release of neuropeptides contribute to the pain experienced after propofol administration, highlighting the involvement of neurogenic inflammation and central sensitization processes.[38]

A study was done in 2014 by Nishimoto et al on mice to know the mechanisms insensory neurons by which propofol causes pain sensation. They concluded that propofol may cause pain sensation through multiple mechanisms involving not only TRPV1 and TRPA1 but also through activation of GABA-A receptor. Both T-type and L-type calcium channels are activated downstream of GABA-A receptor activation by propofol.[13]

Based on the known mechanisms and factors associated with propofol injection pain, several techniques for the prevention of pain have been tried with varying degrees of success. The methods include: site of injection, use of aspirin and other non-steroidal anti-inflammatory drugs, premedication, speed of injection, speed of carrier IV fluid, the use of local anaesthetics, dilution of propofol, different temperatures, opiates, metoclopramide, thiopentone, ketamine, different syringe material and the aspiration of blood. In conclusion, optimizing the technique and conditions of propofol administration plays a crucial role in minimizing the pain experienced by patients.

Briggs et al in 1981 reported a 39% incidence of pain when propofol was injected into the dorsum of the hand, compared to a lower

incidence of 3% when injected into the forearm or antecubital fossa. They also noted that pain was less severe with the emulsion preparation of propofol. Furthermore, they found that pain on injection was higher with a 2% formulation containing Cremaphor EL and ethanol, but reduced with a 1% formulation containing Cremaphor EL alone.[9]

Scott et al in 1988 emphasized the significant influence of injection speed on propofol-induced pain intensity. They observed that slow injection resulted in more pain, likely due to increased concentration and prolonged exposure of propofol to the vein wall. In contrast, rapid injection cleared the drug rapidly from the vein, which may have mitigated pain by allowing immediate mixing with blood.[16]

Liljeroth et al in 2007 demonstrated that intensity of pain increases during venous occlusion at the injection site, without a corresponding increase in the duration of pain. This suggests that pain intensity is more influenced by the concentration of propofol in the blood than by the time of intravascular exposure.[39]

In summary, these studies highlight the importance of injection site selection, formulation type, injection speed, and the concentration of propofol in influencing the incidence and intensity of pain experienced during propofol administration.

Various methods or drugs are used to reduce the pain associated with propofol administration.

Lignocaine is commonly used to prevent pain associated with propofol injection. It works by blocking voltage-gated sodium channels, which are responsible for transmitting pain signals. By blocking these channels, lignocaine prevents the transmission of pain signals from the injection site, thereby reducing or eliminating the pain caused by propofol injection. This mechanism of action is well-established and forms the basis of its effectiveness in clinical practice for this purpose.

Following techniques has been studied-

Pretreatment with lignocaine:

McCulloch and Lees (1985) found that lignocaine 10 mg immediately before propofol injection reduced pain incidence from 37.5% to 17.5%,

but this was not statistically significant.[40] Ganta and Fee (1992) reported a significant reduction in pain incidence from 49.4% to 21.1% with lignocaine 10 mg before propofol injection.[41] Lyons et al (1996) showed that lignocaine 10 mg administered 10 secs before propofol injection reduced pain incidence from 64% to 44%.[42] Ray et al (2011) compared lignocaine, fentanyl, and placebo for pain prevention during propofol injection. They found that lignocaine 40 mg was more effective than fentanyl 100 microgram (mcg) and placebo when retained in tourniquet-occluded veins for 1 minute.[43] Karki et al (2023) studied the efficacy of topical cold thermotherapy (using an ice gel pack) combined with intravenous lignocaine pre-treatment for reducing pain from propofol injection. They concluded that ice gel pack therapy was not superior to lignocaine pre-treatment alone.[44]

These studies collectively suggest that lignocaine, whether administered alone or in combination with other methods, is effective in reducing pain associated with propofol injection. The timing of lignocaine administration, the dose used, and the presence of other premedications (like diazepam) may influence its efficacy.

The use of lignocaine mixed with propofol serves to alleviate pain during propofol injection through several proposed mechanisms:

- Stabilization of Kinin Cascade: Scott et al (1988) suggested that lignocaine may stabilize the kinin cascade, which is involved in pain signaling pathways.[16]

- pH Modification: Eriksson et al (1997) demonstrated that lignocaine mixed with propofol lowers the pH of the solution. This acidity change leads to a lower concentration of free propofol in the aqueous phase, potentially reducing irritation and pain upon injection.[23]

- Clinical Effectiveness: Studies have consistently shown the effectiveness of lignocaine mixed with propofol in reducing the incidence of pain: Brooker et al (1985) reported a decrease in pain incidence from 57% to 27% when using lignocaine 7.5 mg mixed with propofol 142.5 mg before injection.[45]

Nathanson et al (1996) reported a significant reduction in propofol injection pain incidence from 67% to 13% when lignocaine 40 mg was mixed with propofol before injection.[46]

King et al found that lignocaine 20 mg significantly reduced the incidence of injection pain from 73% to 32%. They also observed an inverse relationship between the amount of lignocaine used and the incidence of pain.[47]

Valtonen et al in 1989 demonstrated that lignocaine 10 mg mixed with propofol (at a dose of 2.0–2.5 mg/kg in children) significantly decreased the incidence of pain caused by propofol from 85% to 20%.[48]

These findings underscore the effectiveness of lignocaine when mixed with propofol in reducing the discomfort associated with propofol injection, both in adult and paediatric populations. The varying doses used in these studies suggest that even lower doses of lignocaine can provide substantial pain relief, highlighting its utility across different patient demographics. Overall, mixing lignocaine with propofol is a well-supported technique to mitigate the pain associated with propofol injection, likely through a combination of stabilizing biochemical pathways and modifying the physical properties of the propofol solution.

Comparing lignocaine pre-treatment with lignocaine mixed with propofol reveals several findings from various studies.

Scott et al in 1988 found that mixing lignocaine 10 mg with propofol significantly reduced the incidence of pain from 46.7% to 13.5%, whereas pretreatment with lignocaine 10 mg 30 seconds before propofol injection reduced pain incidence from 46.7% to 40%. This suggests that mixing lignocaine with propofol may be more effective in reducing pain compared to pretreatment alone.[16]

Masaki et al in 2003 examined the mixture of lignocaine and propofol under scanning electron microscopy and cautioned against mixing more than 20 mg of lignocaine with 20 ml of propofol. They noted that larger droplet diameters could pose a risk of fat embolism, particularly if such mixtures are used for long-term infusions.[49]

Lee et al in 1994 compared pretreatment with thiopentone (100 mg) and lignocaine (20 mg) before propofol injection. They found that thiopentone was more effective than lignocaine in reducing propofol injection pain (12% with thiopentone vs. 28% with lignocaine). The mechanism of thiopentone's effectiveness is not fully understood but may involve central or peripheral actions affecting kinins, pH changes, or propofol's pharmacokinetics.[50]

Agarwal et al in 2004 recommended pretreatment with thiopentone (0.5 mg/kg) along with venous occlusion for 1 minute to prevent pain from propofol injection They advocated it for routine use but noted potential drawbacks such as increased rates of postoperative nausea and vomiting, which could prolong recovery times and possibly increase hospital admissions.[51]

In summary, while both pretreatment with lignocaine and mixing with propofol are effective strategies to reduce pain during propofol injection, mixing lignocaine directly with propofol appears to offer a potentially more robust reduction in pain incidence. However, careful attention to safety considerations, especially regarding the potential for fat embolism with larger droplet sizes in mixed solutions, is crucial. Additionally, the choice between lignocaine and thiopentone for pretreatment involves balancing efficacy with potential side effects and patient-specific considerations.

Akbari et al in 2018 compared analgesic effects of ketamine, magnesium sulfate, and thiopentone on propofol injection pain and concluded that ketamine and thiopentone can be effective medications in reducing pain caused by propofol injection. According to the results, magnesium sulfate is not recommended for reducing pain due to propofol injection.[52]

Tan et al's study in 1998 highlighted the efficacy of pretreating with ketamine to reduce pain during propofol injection. Study showed that pretreatment with ketamine 10 mg in 1 ml of normal saline, administered 30 secs before propofol injection, led to a significant decrease in the incidence of pain from 84% to 26%. This demonstrates ketamine's effectiveness in mitigating the discomfort associated with

propofol injection. The researchers proposed that ketamine exerted its effect through a local anesthetic action rather than a central analgesic effect. This distinction is based on the low dose used (< 0.2 mg/kg), which is typically below the threshold for producing significant CNS effects. Instead, ketamine likely acted locally at the injection site to block the transmission of pain signals along the afferent nerve pathways.

Tan et al's findings suggest that ketamine can be a valuable option for preventing propofol injection pain, particularly in situations where other local anaesthetics like lignocaine may not be suitable or effective. The local anaesthetic properties of ketamine make it a promising alternative or adjunct to traditional methods of pain prevention during propofol administration.[3]

Iwata M et al in 2010 did a study which aimed at determining whether ketamine can safely reduce propofol injection pain during anaesthesia induction for lung surgery. They reached to conclusion that 1 mg/ kg of ketamine completely eliminated propofol pain without affecting hemodynamics during start of anaesthesia and oxygenation during one lung ventilation.[53]

Sangwar et al in 2023 evaluated efficacy of low dose IV ketamine for prevention of propofol injection pain. Study concluded that IV ketamine in a dose of 100mcg/kg with tourniquet given before propofol is useful in decreasing pain's incidence and intensity significantly without any adverse haemodynamic effect.[54]

Inhalational agents like nitrous oxide (N2O) and sevoflurane have been explored for their ability to reduce pain associated with propofol injection, primarily due to their central analgesic effects.

DeSousa in 2011 demonstrated a three-fold action of sevoflurane in reducing pain during propofol injection: Sevoflurane has intrinsic analgesic properties that act centrally to reduce pain perception. It also acts as a sedative, potentially reducing anxiety and discomfort related to injection procedures. Sevoflurane's peripheral vasodilatory effects can reduce the pain associated with the injection into smaller vein.The study used sevoflurane 3% during preoxygenation before the injection

of fentanyl and propofol. When combined with lignocaine, sevoflurane completely abolished pain upon propofol injection in all patients.[55]

Kim et al in 2013 studied N_2O and found that pretreatment with inhaled 67% N_2O reduced pain not only during propofol injection but also during rocuronium injection. Furthermore, N_2O, whether used alone or in combination with lignocaine, was found to be superior to lignocaine alone in decreasing pain associated with propofol injection.[56]

These findings highlight the potential of inhalational agents like sevoflurane and N_2O as effective strategies to mitigate the discomfort of propofol injection. Their central analgesic effects, combined with other properties like sedation and vasodilation, contribute to their efficacy in clinical settings. Combining these agents with traditional local anesthetics such as lignocaine can enhance pain relief and improve patient comfort during procedural anesthesia.

The use of opioids like alfentanil and fentanyl as pretreatment to reduce pain during propofol injection has been studied extensively. Helmers et al in 1990 found that pretreatment with alfentanil 0.5 mg significantly reduced the incidence of propofol injection pain from 40% to 16%.[57]

Fletcher et al in 1994 and Nathanson et al in 1996 reported similar findings with pretreatment using alfentanil 1 mg administered 15 and 30 secs before propofol injection, respectively. They observed significant reductions in pain incidence from 84% to 36% and from 67% to 24%.[58, 46]

Bahar et al in 1982 found that fentanyl 0.1 mg administered 3-5 mins before propofol injection reduced the severity of pain but did not consistently reduce its overall incidence. This discrepancy might be attributed to differences in propofol formulations used (Cremophor EL vs soybean emulsion) and the small sample size (10 patients).[59]

Helmers et al in 1990, in contrast, reported a significant decrease in the incidence of propofol injection pain from 40% to 16% with fentanyl use. They studied a larger cohort (50 patients) and used a different propofol formulation (soybean emulsion).[57]

Overall, these studies indicate that opioids such as alfentanil and fentanyl can effectively reduce pain during propofol injection when administered as pre-treatment. The timing of administration, dose, and type of propofol used may influence the outcomes. Larger studies and standardized protocols are necessary to further clarify the optimal use of opioids in this context, ensuring improved patient comfort during anaesthesia induction.

Lyons et al in 1996 demonstrated that administering pethidine 25 mg 10 secs before propofol injection significantly reduced both the severity and incidence of propofol injection pain. They reported a decrease in pain incidence from 64% to 35%. They also noted that pethidine appeared to be more effective in women, possibly due to the higher dose per kg of body weight in women compared to men. The study suggested that besides its local anesthetic and analgesic effects, pethidine might have different pharmacodynamic effects between gender.[42]

Kizilcik et al in 2014 studied the effects of a fentanyl-propofol mixture on propofol injection pain. They found that mixing fentanyl with propofol significantly reduced injection pain compared to both a control group and a group where fentanyl was administered as pretreatment. This indicates that combining fentanyl directly with propofol is an effective strategy for pain management during propofol injection.[60]

These studies underscore the effectiveness of opioids like pethidine and fentanyl in reducing the discomfort associated with propofol injection. The mechanisms likely involve their analgesic properties, which act centrally to alleviate pain perception. Moreover, the direct mixing of fentanyl with propofol offers a convenient and effective approach to preemptively manage injection related pain during anaesthesia induction.

Wang et al in 2020 compared IV nalbuphine and lidocaine in mitigating propofol induced injection pain during gastroscopy. They concluded that pretreatment with nalbuphine 0.1 mg/kg was effective in decreasing propofol induced injection pain and propofol consumption.

Propofol combined with nalbuphine can be safely and effectively used during gastroscopy.[61]

Remifentanil, an opioid with unique pharmacokinetic properties, has been extensively studied for its effectiveness in reducing propofol-induced pain. In a randomized double-blinded trial, pretreatment with remifentanil (35 mcg/kg/min for 30 secs) and propofol premixed with lignocaine (in a 10:1 ratio) individually resulted in a similar incidence of propofol-induced pain (37.8%). However, when remifentanil pretreatment was combined with lignocaine-propofol mixture, the incidence of propofol-induced pain significantly decreased to 8.7%. This combination demonstrated superior pain reduction compared to either remifentanil or lignocaine-propofol mixture alone. In another randomized double-blinded prospective trial, remifentanil was compared with lignocaine, metoclopramide, and ketamine for reducing propofol-induced pain. The study found that lignocaine and metoclopramide were more effective than remifentanil and ketamine in reducing pain associated with propofol injection. This suggests that while remifentanil is effective, other agents like lignocaine and metoclopramide may offer greater efficacy in this context. A study by Aouad et al showed that combining pretreatment with remifentanil and premixing propofol with lignocaine abolished moderate and severe pain completely and significantly reduced mild pain associated with propofol injection. This combination approach highlights the synergistic effect of using remifentanil for its central analgesic properties and lignocaine for its local anaesthetic effects, achieving comprehensive pain relief during propofol administration.[62]

In summary, remifentanil is frequently studied and used in clinical trials due to its rapid onset and short duration of action, making it suitable for managing propofol-induced pain. When combined with lignocaine or other agents, remifentanil can significantly reduce or even eliminate pain associated with propofol injection, improving patient comfort during anaesthesia induction.

The use of NSAIDs (Non-steroidal anti-inflammatory drugs) such as acetyl salicylic acid (aspirin), ketorolac, and diclofenac has been

explored for their potential to reduce pain associated with propofol injection. Bahar et al in 1982 demonstrated that pretreatment with IV acetyl salicylic acid 1 g given 15 mins before propofol injection significantly reduced the incidence of severe pain from 70% to 20%. However, it did not reduce the overall incidence of pain. This suggests that while aspirin may have some effect on severe pain, its efficacy in preventing overall pain from propofol injection is limited.[59]

Smith and Power in 1996 studied the effect of ketorolac 10 mg administered immediately before propofol injection. They found that there was no significant difference in the incidence of pain between the group given ketorolac and the control group not given ketorolac. They speculated that ketorolac might not effectively block local vascular endothelial prostaglandin synthesis or that prostaglandins might not play a significant role in the pain caused by propofol injection. They also suggested that a longer time interval might be needed for ketorolac to exert its effect.[63]

Mohta et al in 2004 investigated the efficacy of diclofenac as a pretreatment for reducing moderate to severe pain following propofol injection. They found that both 15 mg and 25 mg doses of diclofenac, administered 30 secs before propofol injection, significantly reduced the incidence of moderate to severe pain. The efficacy of diclofenac pretreatment was comparable to that of ketorolac in other studies. However, they noted that diclofenac itself could cause mild pain in some patients when administered in a 5 ml volume, suggesting that this dilution might not be optimal for pretreatment.[64]

While NSAIDs like diclofenac show promise in reducing pain associated with propofol injection, the optimal dosing and timing need further investigation. Studies suggest that the effectiveness of NSAIDs may vary, possibly due to differences in their mechanism of action on prostaglandin synthesis and the specific pain pathways involved in propofol injection pain.

- Further research is warranted to explore different dilutions of diclofenac and to determine the ideal time interval between NSAID

administration and propofol injection to maximize pain relief while minimizing potential adverse effects.

5-HT3 receptor antagonists have been commonly used to reduce propofol injection pain. Wang et al in 2016 did meta-analysis to evaluate the efficacy and safety of 5-HT3 receptor antagonists in decreasing the incidence and intensity of propofol injection pain. A total of eight Randomized Controlled Trials were included in the finalanalysis.Their meta-analysis indicated that 5-HT3 receptor antagonists can effectively reduce the incidence and severity of propofol injection pain. Additionally, 5-HT3 receptor antagonists may become the alternatives to lidocaine in attenuating propofol injection pain.[12] However, evidence is still limited for the safety of 5-HT3 receptor antagonists on propofol injection pain.

Ramosetron is a recently developed 5HT3 receptor antagonist. Singh et al in 2014 compared lidocaine and ramosteron for preventing propofol pain. They concluded that IV ramosetron when given as pretreatment is as effective as lidocaine on propofol associated pain with an added advantage of preventing post operative nausea and vomiting.[65]

Metoclopramide, primarily known as an anti-emetic, has also been recognized for its potential to reduce pain associated with propofol injection. Ganta and Fee in 1992 conducted a study where they administered metoclopramide 5 mg immediately before propofol injection into a dorsal hand vein. They compared the effectiveness of metoclopramide to lignocaine 10 mg and normal saline in reducing propofol injection pain. Their findings indicated that metoclopramide was equally effective as lignocaine in decreasing the incidence of pain associated with propofol injection. The researchers postulated that metoclopramide's action may involve reducing spasm in the veins, contributing to its analgesic effect in this context.[41]

Polat et al in 2012 also investigated the pain reducing effects of metoclopramide after propofol injection. They found that metoclopramide had a similar effect to lignocaine in alleviating pain following propofol administration. This study further supported the

notion that metoclopramide can effectively mitigate propofol injection pain, possibly through mechanisms beyond its anti-emetic properties. The findings from these studies suggest that metoclopramide can be a viable alternative or adjunct to lignocaine in managing propofol injection pain, particularly in scenarios where local anaesthetics are contraindicated or unavailable.[66]

Cisatracurium, a nondepolarizing skeletal muscle relaxant used to induce neuromuscular blockade, has shown promise in reducing pain associated with propofol injection.They exert their effects by blocking acetylcholine receptors at the neuromuscular junction, leading to skeletal muscle relaxation. Beyond their primary action, these agents can also affect sensory nerve endings, nerve trunks, and possibly muscle spindles.

Mudhelli et al in 2021 conducted a study to evaluate the effectiveness of cisatracurium in preventing propofol-induced pain. They administered cisatracurium at a dose of 0.15 mg/kg into veins occluded by a tourniquet before propofol injection. The study concluded that this pretreatment significantly reduced both the incidence and severity of pain caused by propofol injection. Importantly, no significant complications related to cisatracurium administration were reported in patients undergoing general anaesthesia induced by propofol. The reduction in propofol injection pain with cisatracurium pretreatment could be attributed to its effect on peripheral nerve endings and nerve trunks.[67]

In conclusion, cisatracurium has shown effectiveness in reducing both the incidence and severity of pain associated with propofol injection, likely through its actions on peripheral nerve endings and nerve trunks. This makes it a valuable addition to strategies aimed at improving patient comfort during anesthesia induction with propofol.

Alpha 2-adrenoreceptors located on blood vessels inhibit norepinephrine release, resulting in release of prostaglandins and cause vasodilation that antagonize the vasoconstrictor response. Dexmedetomidine has been shown to promote peripheral antinociception. Therefore dexmedetomidine can also be used for relief

of propofol pain. Ayoglu et al in 2007 compared dexmedetomidine with lignocaine for their effect on reducing pain due to propofol and rocuronium and concluded that dexmedetomidine failed to decrease propofol injection pain but reduced rocuronium withdrawal movement.[68]

Sapate et al. in 2013 studied effect of injection dexmedetomidine for decreasing incidence of propofol pain and compared it with injection lignocaine. They reported that dexmedetomidine is equally effective and can be used as an alternative to lignocaine for relief of propofol injection pain without any significant side effects.[69]

Clonidine is an analgesic, sedative and anxiolytic. Along with local anaesthetic agents, it is an adjunct in regional anaesthesia. Deverakonda et al in 2018 studied clonidine for propofol induced pain. They reported that 0.5 mcg/kg of clonidine is effective in reducing propofol induced pain. It also did not cause significant hemodynamic adverse side effects.[70]

In the study by Sultana et al in 2021, the comparative antinociceptive effects of dexmedetomidine and clonidine immediately before propofol injection were evaluated for their efficacy in reducing propofol injection pain. They administered dexmedetomidine at a dose of 0.5 mcg/kg and clonidine at the same dose (0.5 mcg/kg) immediately before propofol injection and found that dexmedetomidine was more effective than clonidine in alleviating both the incidence and severity of propofol injection pain.This suggests that dexmedetomidine has superior antinociceptive properties compared to clonidine when used as a premedication specifically to reduce propofol-induced pain. [71]

McCrirrick and Hunter in 1990 investigated the impact of lowering the temperature of propofol to 4°C.They observed a significant reduction in the incidence of propofol injection pain, from 46% to 23%.The researchers hypothesized that the lower temperature might slow down the kinin cascade, a biochemical process involved in pain sensation.[20]

Fletcher et al in 1996 focused on warming propofol to 37°C (body temperature).They reported a notable decrease in the incidence of propofol injection pain, from 59% to 22%. Their suggested mechanisms included the possibility that the higher temperature could influence the

release of pain mediators. Additionally, they proposed that temperature might affect the partition coefficient of propofol, altering its distribution and concentration in the solution.[21]

Terada et al in 2014 explored the use of topical cooling as a method to reduce propofol injection pain. They found that topical cooling alone decreased the incidence of pain from 39% to 17%. When combined with lignocaine, the incidence further dropped to 8%. This study highlighted that cooling the skin surface where propofol is injected can effectively alleviate pain, possibly by reducing local nerve sensitivity or altering the perception of pain.[72]

In conclusion, temperature manipulation, whether cooling or warming, presents viable strategies to mitigate propofol injection pain, offering clinicians options to tailor anaesthesia practices to individual patient needs and preferences.

Klement and Arndt in 1991 investigated the effect of diluting propofol with 10% intralipid vs 5% glucose. They found that dilution with 10% intralipid was more effective than 5% glucose in reducing propofol injection pain. Pain intensity was shown to increase with higher concentrations of propofol in the aqueous phase. Intralipid, being a lipid emulsion, reduces the concentration of propofol in the aqueous phase, thereby lowering the incidence and severity of pain associated with propofol injection.[17]

Doenicke et al in 1996 demonstrated that propofol injection pain could be further reduced by using higher concentrations of fat emulsion (intralipid) in the propofol formulation. This suggests that increasing the proportion of lipid in the propofol formulation decreases the concentration of propofol in the aqueous phase, leading to less pain upon injection.[18]

The pain associated with propofol injection is believed to be linked to the concentration of propofol in the free aqueous phase. Higher concentrations can cause irritation to blood vessel walls and sensory nerve endings, resulting in pain. Intralipid forms a lipid layer around the propofol molecules, reducing their concentration in the aqueous phase where they can cause irritation. Glucose, on the other hand, does not

alter the concentration of propofol in the aqueous phase to the same extent as intralipid, hence its effectiveness in reducing pain is comparatively lower.

In summary, the studies by Klement and Arndt, as well as Doenicke et al., highlight the significant impact of propofol dilution on injection pain. [17, 18]

Diprivan is the commonly used formulation of propofol, which typically contains propofol in an emulsion with soybean oil and egg lecithin. It has a pH range of 7.0–8.5. Ampofol is a newer formulation with a lower lipid content, specifically containing propofol 1%, soybean oil 5%, and egg lecithin 0.6%. It has a lower pH range of 5.5–7.0. Dajun et al in 2004 studied Ampofol with Diprivan for propofol Induced pain. They found that despite administering lidocaine 1.5 minutes before propofol injection, the overall incidence of pain was higher in the Ampofol group (39%) compared to the Diprivan group (9%). The study suggested that the higher incidence of pain with Ampofol could be related to a decrease in the lipid content of the emulsion. Lower lipid content may increase the free fraction of propofol in the aqueous phase, which could irritate blood vessel walls and nerve endings, thereby increasing pain. Interestingly, despite Ampofol having a lower pH, it did not result in more severe pain compared to Diprivan. This contrasts with the expectation that lower pH might exacerbate pain sensation. The study underscores the importance of emulsion composition in determining the pain associated with propofol injection. Emulsions with higher lipid content, such as those containing medium chain triglycerides (MCT), tend to result in less injection pain. In conclusion, while Ampofol represents a newer formulation with reduced lipid content and a lower pH compared to Diprivan, it was associated with a higher incidence of pain upon injection. This highlights the complex relationship between propofol formulation, lipid content, pH, and injection pain, warranting careful consideration in clinical practice and further research for optimization.[73]

Lomax et al in 1994 suggested that propofol injection pain could be attributed to irritant substances produced when propofol interacts with

plastic disposable syringes. By using glass syringes instead of plastic, they observed a significant reduction in the incidence of pain from 33% to 16%. This finding implies that the materials used in syringes can influence the properties of propofol and its interaction with tissues upon injection.[74]

McDonald and Jameson in 1996 investigated the buffering effect of blood on propofol injection pain. They found that aspirating 2 ml of the patient's blood into the syringe containing propofol before injection significantly reduced pain compared to adding 2 ml of saline. Specifically, the incidence of pain was 13% with blood buffering, 58% with saline, and 18% with lignocaine 20 mg added to propofol. The authors speculated that the buffering effect of blood might alter the free aqueous concentration of propofol or reduce the initial release of kinins triggered by propofol injection. This suggests that blood could mitigate the chemical irritation caused by propofol in the blood vessels.[75]

Jalota et al in 2011 analysed data from 177 randomised controlled trials totalling 25260 adults and found that overall risk of pain from propofol injection alone was about 60%. They conducted a study to determine the most efficacious approach for decreasing propofol injection pain. In their study, they used various drugs like lidocaine-propofol admixture; pre-treatment with lidocaine, various opioids, ketamine, NSAIDS, modified propofol formulations containing long chain triglycerides and non drug category incorporating techniques such as varying temperature of propofol and venous occlusion. They discovered that the two most effective methods to reduce pain during propofol injection were either using the antecubital vein or pretreating with lidocaine while applying venous occlusion when opting for the hand vein.[76]

HES comprises of a family of semisynthetic, polydisperse colloid solutions made up of large ethylated, polymerized amylopectin molecules. Colloids are used for intraoperative fluid therapy in anaesthesia. They are considered to be safe.

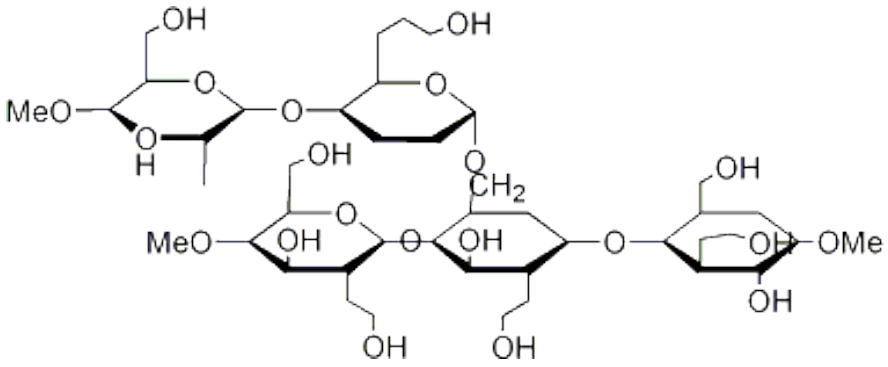


Figure 2: Structure of hydroxyethyl starch

They are macromolecules that have the capacity to modify endothelial cell junctions and permeability of the vascular endothelium and inhibit endothelial activation by various substances and molecules. Thus, pre-administration of colloids may prevent contact activation by propofol, which may in turn lead to reduced pain during injection. This modification of the endothelium by starches has been proven in a wide variety of experimental models using both in-vivo and in-vitro testing. In a porcine model of cerebral ischaemia, IV administration of 10% HES 257/0.47 just after ischaemia (600 mg/kg) and continued during the period of reperfusion (600 mg/kg/h) resulted in a significant reduction in the number of leucocytes adhered to the cerebral venular endothelium at one and two hours following reperfusion. This lower capillary permeability was connected with the reduced leucocyte adherence that was observed.[77] In a similar manner, isovolaemic haemodilution with 6% HES 200/0.62 to a 30% haematocrit resulted in a 40% drop in the number of post-ischaemic neutrophils adhered to postcapillary skeletal muscle venules throughout the two hours after reperfusion.[78]

Prasad in 2018 studied the effect of 6% HES pre-administration for reduction of pain on propofol injection. In the study, 100 patients were recruited, 50 of them were assigned to the HES group and 50 to the NS group. 100ml bolus of HES or 0.9% saline was administered over three to five mins through an 18 gauge cannula placed in the hand or forearm vein, followed by induction with 1% propofol premixed with 2% lidocaine. They assessed pain during propofol injection every 10 secs before the loss of verbal command. Pain was perceived as 0-no pain; 1-mild pain evident only on questioning after 10 secs without any

obvious discomfort; 2-moderate pain self reported by patients within 10 secs with some discomsfort and 3-severe pain accompanied by withdrawing of hand and behavioural signs. The incidence of discomfort was considerably greater in the NS group compared to the HES group (50% vs 30%). The incidence of severe pain was greater in the NS group (6% vs 0%), and the incidence of moderate pain was higher in the NS group (14% vs 6%), while the incidence of mild pain was equivalent (30% vs 24%; NS vs HES). The extent of the difference in pain experienced by each group was significant. In conclusion, when compared to injecting with normal saline, the discomfort associated with injecting propofol is greatly mitigated by the pre-administration of 100 mL of 6% HES 130/0.4 three to five mins before administering propofol.[29]

Misra et al in 2022 studied 6% HES preadministration for reduction of pain on propofol injection. The study was done on 126 ASA 1 and 2 patients, 18-65yrs old patients. 100ml bolus of HES or 0.9% saline was administered over three to five minutes through an 18 gauge cannula placed in the hand or forearm vein, followed by induction with 1%propofol premixed with 2% lidocaine. They assessed pain during propofol injection every 10 secs before the loss of verbal command. Pain was perceived as 0-no pain; 1-mild pain evident only on questioning after 10 secs without any obvious discomfort; 2-moderate pain self reported by patients within 10 secs with some discomsfort and 3-severe pain accompanied by withdrawing of hand and behavioural signs. They noted a significantly higher incidence of pain in the normal saline group compared to the HES group (53% vs 28%). Specifically, severe (8% vs 0%) and moderate pain (16% vs 5%) were more prevalent in the normal saline group, whereas the incidence of mild pain was similar between the two groups (29% vs 23%; normal saline vs HES).[30]

There was also a notable difference in the severity of pain between the two groups. Thus, they concluded that pre administration of 100ml bolus of 6% HES 130/0.4 significantly reduced propofol injection pain.[30]

As propofol induced pain is still prevelant in patients undergoing

general anaesthesia, studies on remedies which can prevent this are still lacking. Moreover, HES in relation to alleviation of propofol induced pain has not been studied extensively.

Thus we hypothesised that a multimodal technique utilising co administration of 6% HES to 2% Lignocaine will alleviate pain on propofol injection in a more effective manner. Furthermore use of a NRS scale would have higher objectivity in measuring pain intensity. Hence we propose to comparatively evaluate the incidence and severity of propofol injection pain after preadministration of 6% HES with 2% lignocaine versus 0.9% saline with 2% lignocaine in patients undergoing anaesthesia induction with 1% propofol.

MATERIALS AND METHODS

SOURCE OF DATA

A randomized study was conducted in Department of Anaesthesiology of Dayanand Medical College and Hospital, Ludhiana after approval by Institutional Ethics Committee. A written informed consent was obtained from each patient.

METHOD OF COLLECTION OF DATA

All the patients fulfilling the inclusion and none of the exclusion criteria were included in the study. A total of 206 ASA I and II patients of age 18-65 yrs of either gender undergoing elective surgery under general anaesthesia were selected for the study and were randomly allocated to either of two study groups (Group H and Group S) containing 103 each.

GROUP ALLOCATION

Patients were randomly allocated to either of two study groups based on computer generated randomisation codes.

GROUP H (6% HES with 2% lignocaine)

A total of 103 patients in group H were given a total IV bolus of 50 ml of 6% HES mixed with 2% Lignocaine (1 mg/kg) over 2 mins before induction with Propofol (1%) injection.

GROUP S (0.9% Saline with lignocaine)

A total of 103 patients in group S were given a total IV bolus of 50 ml of 0.9% Saline mixed with 2% lignocaine over 2 mins before induction with Propofol (1%) injection.

The randomization scheme using computer generated random number was prepared by our biostatistician and kept in sealed sequentially numbered envelopes.

The allocation envelope was opened by an anaesthesiologist who was not involved with the direct clinical care of the patient and prepared the drugs as per random allocation sequence and handed

the sterile study drugs syringes to the anaesthesiologist giving drugs to the patient. The anaesthesiologist administering the drug and the observer recording pain measurements were unaware of the nature of the study drug. These codeswere decoded at the end of study period.

Inclusion Criterion

Adult patients of the ASA physical status I and II, 18-65 years old, of either gender and undergoing elective surgery under general anaesthesia.

Exclusion Criterion

- Known history of allergy to propofol or HES
- Emergency surgeries or hemodynamically unstable patients
- Patients in whom hand or forearm veins will not be accessible
- Uncontrolled Hypertensive and diabetic patients
- Patients with history of dyspnoea or NYHA (New York Heart Association) III or IV
- Patients with elevated serum creatinine
- Patient refusal

TECHNIQUE

Pre Anaesthesia Checkup

All patients underwent routine thorough pre anaesthesia checkup one dayprior to surgery consisting of detailed history, co-morbidities, allergy to any drug especially Propofol, Lignocaine and HES. Physical and systemic examinations were done and relevant investigations were noted. Patients were explained that they will receive an IV anaesthetic drug for induction that might cause pain on injection.

To prevent the pain, a drug will be given to the patient according to our study protocol. The patients were instructed to inform the anaesthesiologist of the amount of pain they experienced every 15 secs using a NRS from 0-10 with 0-being no pain and 10-most

excruciating pain. In addition, the patients were educated on the use of NRS scale. The patients were also instructed to inform the anaesthesiologist regarding the amount of pain by using fingers of both hands with each finger assigned one point. Written informed consent was taken from all participants of the study.

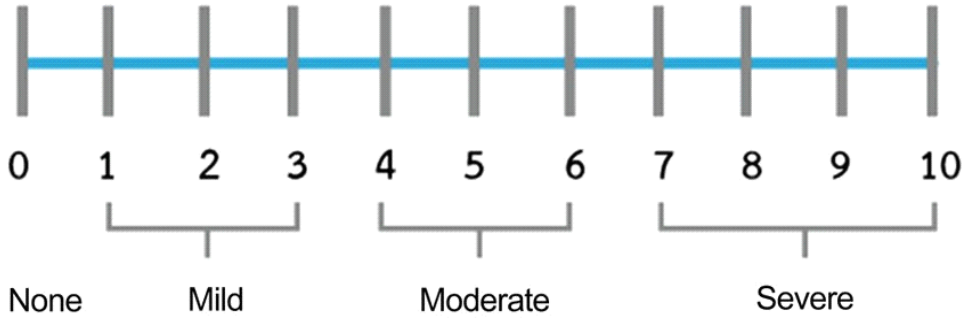
Anaesthesia Technique

In the pre-operative room, after reviewing the investigations and confirmation of fasting and consent, patients were shifted to the operatingroom.

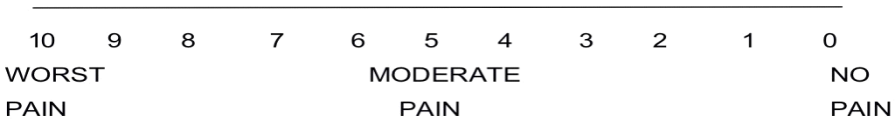
On arrival in the operating room, monitors like pulse oximeter, non invasive blood pressure (NIBP), and five lead Electrocardiography were attached. 3 readings of Heart Rate (HR), NIBP, SpO2 (Saturation of peripheral oxygen) were recorded and the mean was calculated and was considered as baseline reading. An 18G cannula was inserted either on the dorsum of hand or forearm veins. No premedication was given to any patient. Patients were pre-oxygenated with 100% oxygen for three minutes.

The study drugs 6% HES (Expavon®- NEON) mixed with 2% Lignocaine (Loxicard®-NEON) (1 mg/kg) or 0.9% Saline with 2% Lignocaine (total volume-50ml) was drawn up in 50 ml syringe (Romsons®) by an Anaesthesiologist not involved in the study and was handed over to the Anaesthesiologist who administered it to the patient over a period of two minutes.

After administration of the study drug, 1% Propofol (Fresofol® 1% MCT/Long Chain Triglycerides) (2 mg/kg) was administered at the rate of 0.5ml/sec for the induction of anaesthesia. Pain scoring using NRS was assessed every 15 secs before the patient lost response to verbal commands. The NRS scale was used to determine the severity of the discomfort from 0-10, with 10 being the most severe. After induction and confirmation of mask ventilation, rest of anaesthesia administration was continued as per standard protocols.



NUMERICAL RATING SCALE



OUTCOME: Following outcomes were observed:

- Incidence of pain on propofol injection
- Severity of pain on propofol injection using NRS.

SAMPLE SIZE CALCULATION

By using previous study (Satyajeet misra et al 22), the Incidence of Pain is 53% in NS group and 28% in HES group

Based on this assumption

The formula used in the situation is as under:

n = [Z 1- α/2 √2 P (1-P) + Z 1- β .√{P1(1-P1) + P2 (1-P2)}] 2(P1-P2) 2

Where P=(P1+P2)/2

- Approximate value of efficacy/cure rate for standard treatment =P1
- Approximate value of efficacy/cure rate for other treatment = P2
- Effect size = (P2-P1)
- Level of significance (usually 5%)
- Zα = Value of standard normal variate corresponding to α level ofsignificance (1.96)

· Zβ = The standard normal deviate for desired power (0.842)

With the above assumptions the sample size for 95% confidence level &95% power worked out 94 in each study group. To reduce the margin of error, total sample size was taken as 206 (103 subjects in each group).

STATISTICAL ANALYSIS

Data was described in terms of range; mean ± standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. To determine whether the data is normally distributed, a Kolmogorov-Smirnov test was used. Comparison of quantitative variables between the study groups were done using Student t-test and Mann Whitney U test for independent samples for parametric and non-parametric data respectively. For comparing categorical data, Chi square ($\chi 2$) test was performed and fisher exact test was used when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using (Statistical Package for the Social Science) SPSS 21version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

OBSERVATIONS AND RESULTS

The present study was conducted in a randomized, double blinded manner in the Department of Anaesthesiology, Dayanand Medical College and Hospital on a total of 206 ASA grade I and II adult patients of either gender, aged 18-65 yrs scheduled for elective surgeries under general anaesthesia.

Figure 3: CONSORT flow diagram of the study

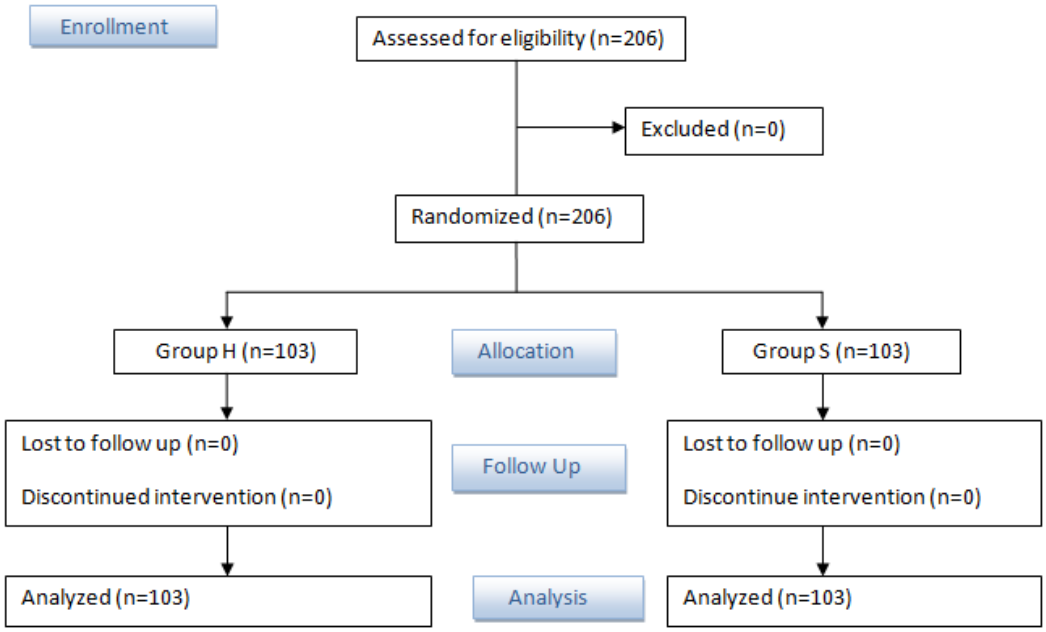


TABLE 1: DEMOGRAPHIC PROFILE: DISTRIBUTION OF SUBJECTS ACCORDING TO AGE, WEIGHT, BMI, GENDER, ASA PHYSICAL STATUS

Table 1a: Distribution according to Age, Weight and BMI

	Group H		Group S		Z	p-value
	Mean	SD	Mean	SD		
AGE	38.50	12.65	40.24	12.58	-1.023	0.306
WEIGHT(kg)	69.46	11.99	71.46	11.18	-0.697	0.486
BMI (kg/m2)	25.44	3.60	25.96	3.52	-0.556	0.579

Table 1b: Distribution of subjects according to Gender

		Group H		Group S		Total	Chi-square value	p-value
		No. of cases	% age	No. of cases	% age			
GENDER	F	56	54.4%	54	52.4%	110	0.078	0.780
	M	47	45.6%	49	47.6%	96		
Total		103	100.0%	103	100.0%	206		

Table 1c: ASA Physical Status

		Group H		Group S		Total	Chi-square value	p-value
		No. Of Cases	% age	No. of cases	% age			
ASA	I	49	47.6%	48	46.6%	97	0.019	0.890
	II	54	52.4%	55	53.4%	109		
Total		103	100.0%	103	100.0%	206		

Mean age in Group H was 38.50 ± 12.65 years and in Group S it was 40.24 ± 12.58 years. Mean weight in Group H was 69.46 ± 11.99 kilograms and in Group S it was 71.46 ± 11.18 kilograms. Mean BMI being 25.44 ± 3.60 kilogram/metre^2 and 25.96 ± 3.52 kg/m^2 in Group H and S respectively.

Both the groups were statistically comparable with respect to the age, weight and BMI.

In Group H, 54.4% of the patients were females and in Group S, 52.4% were females. The distribution of subjects across both the groups was comparable.

In Group H, 47.6% of patients were ASA I and 52.4% were ASA II and in Group S, 46.6% of patients were ASA I and 53.4% were ASA II. Both the groups were statistically comparable with respect to ASA class of physical status.

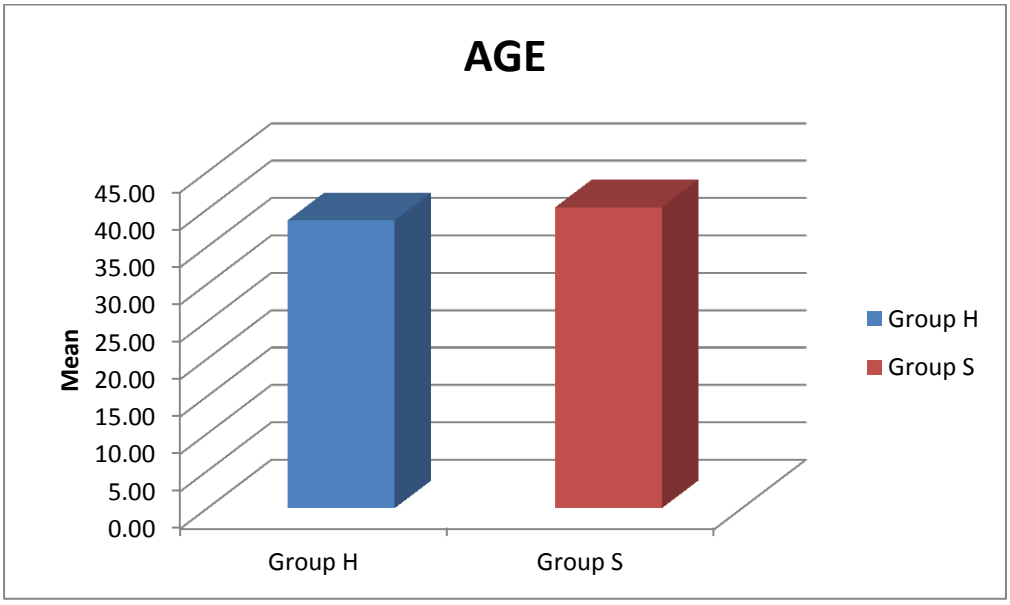


Figure 4: Mean Age Distribution

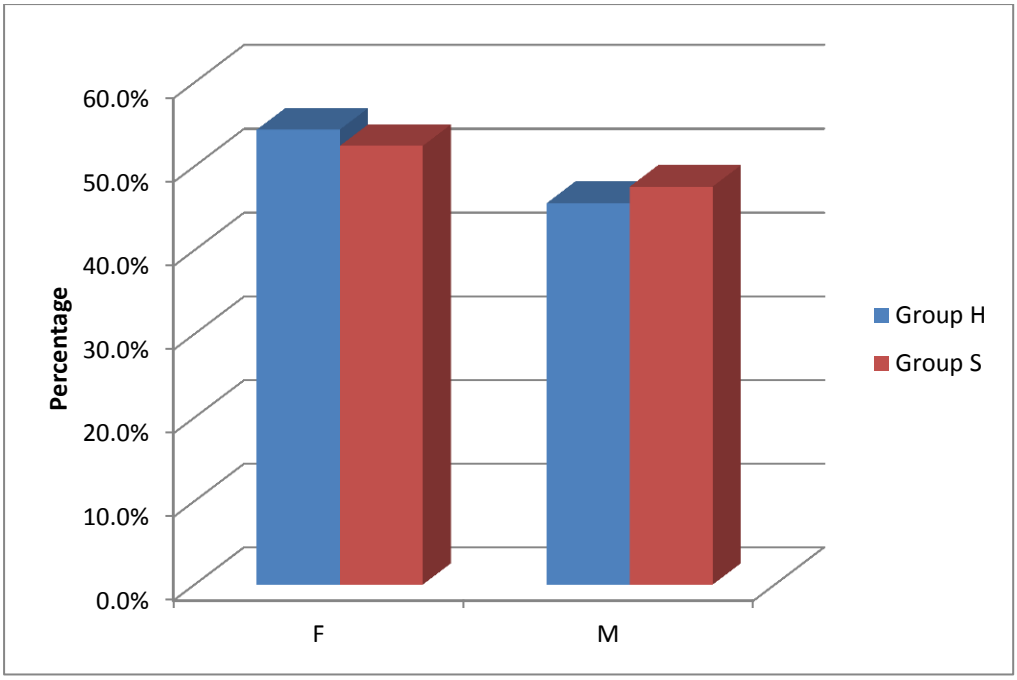


Figure 5: Gender

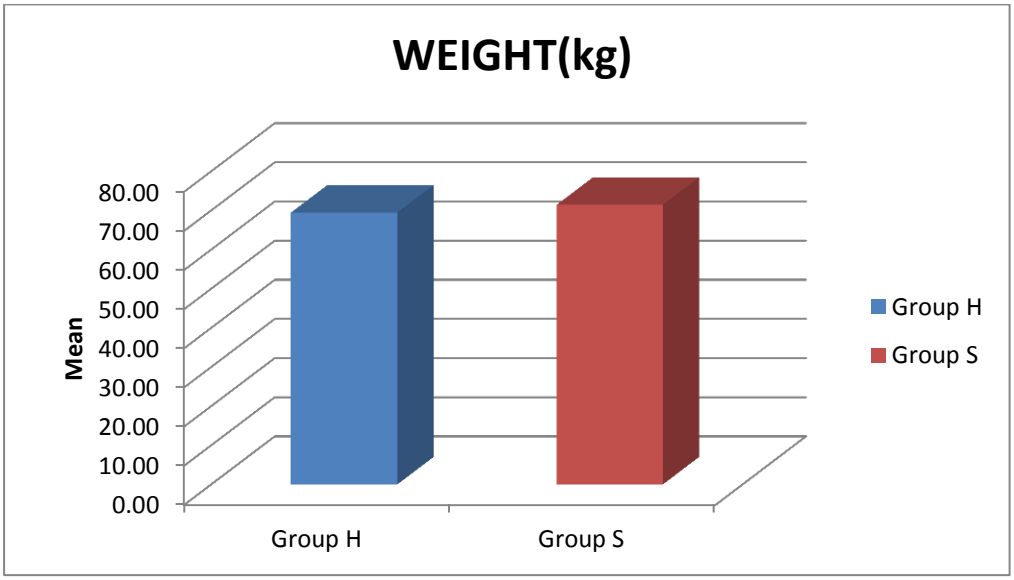


Figure 6: Mean Weight

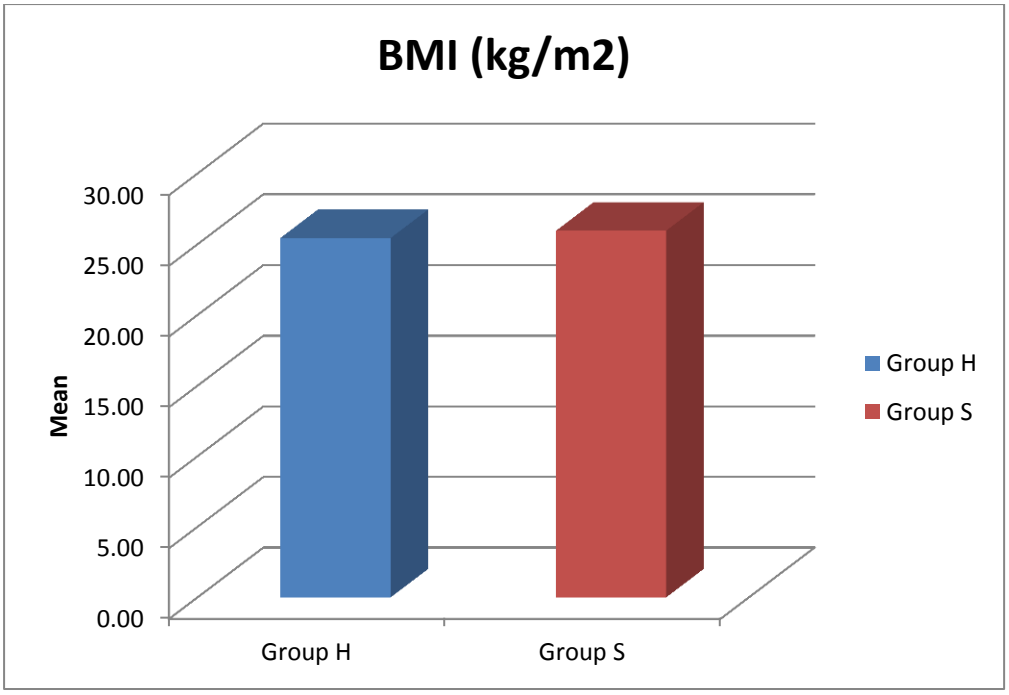


Figure 7: Mean Body Mass Index (BMI)

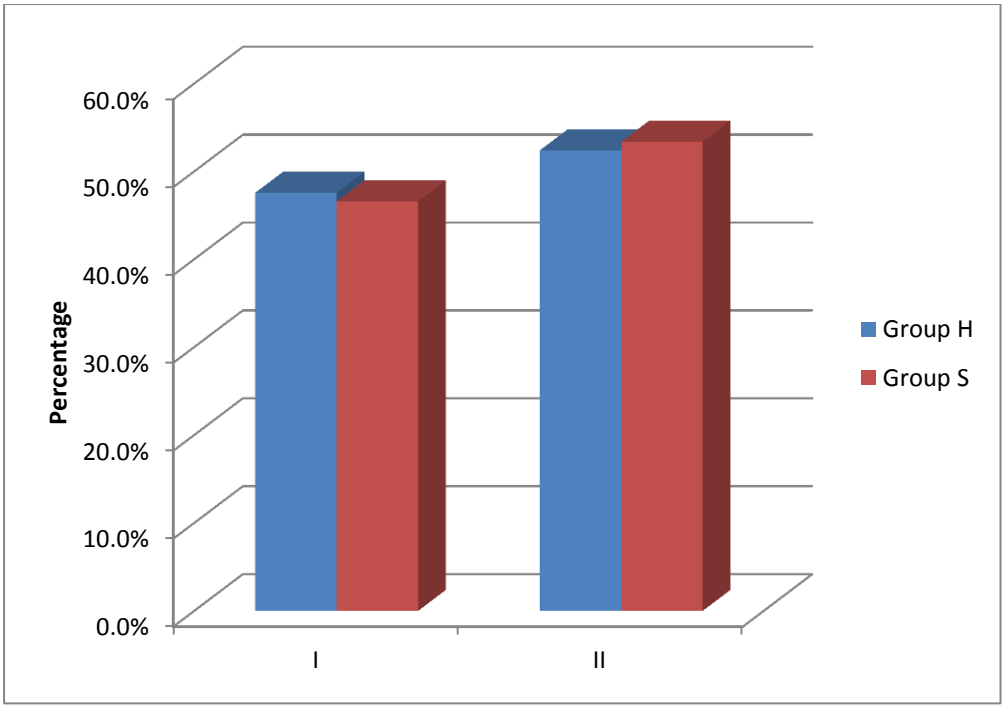


Figure 8: ASA Physical Status

TABLE 2: HAEMODYNAMIC PARAMETERS

	Group H		Group S		Z	p-value
	Mean	SD	Mean	SD		
HEART RATE(/min)	83.69	12.55	82.28	12.73	-0.973	0.330
SBP(mm Hg)	122.64	10.54	124.01	10.43	-0.933	0.351
DBP (mm Hg)	77.79	8.56	78.13	8.16	-0.566	0.571
SPO2 (%)	98.27	0.82	98.12	0.69	-1.552	0.121

Vitals of patients in pre-operative area at one minute interval for 3 minutes were noted and mean of vitals was calculated. Mean HR of patient in Group H was 83.69 ± 12.55 per minute and in Group S was 82.28 ± 12.73 per minute.

The mean systolic blood pressure (SBP) in Group H was 122.64 ± 10.54 mm Hg and in Group S was 124.01 ± 10.43 mm Hg.

The mean diastolic blood pressure (DBP) in Group H was 77.79 ± 8.56 mm Hg and in Group S was 78.13 ± 8.16 mm Hg.

The mean SpO2 in Group H was 98.27 ± 0.82 % and in Group S was 98.12 ± 0.69 %.

Both the groups were statistically comparable with respect to preoperative vital parameters.

TABLE 3: Incidence of pain

Table 3A: Incidence of pain before giving Study Drug

		Group H		Group S		Total	Chi-square value	p-value
		No. of cases	% age	No. of cases	% age			
Before giving Study drug	No	84	81.6%	79	76.7%	163	0.735	0.391
	YES	19	18.4%	24	23.3%	43		
Total		103	100.0%	103	100.0%	206		

In Group H, 18.4% of patients had pain at cannula site before administering the study drug. While in Group S, 23.3% of patients had pain at cannula site before administering the study drug. Both the groups were statistically comparable with respect to pain at cannula site before administering the study drug (p value- 0.391).

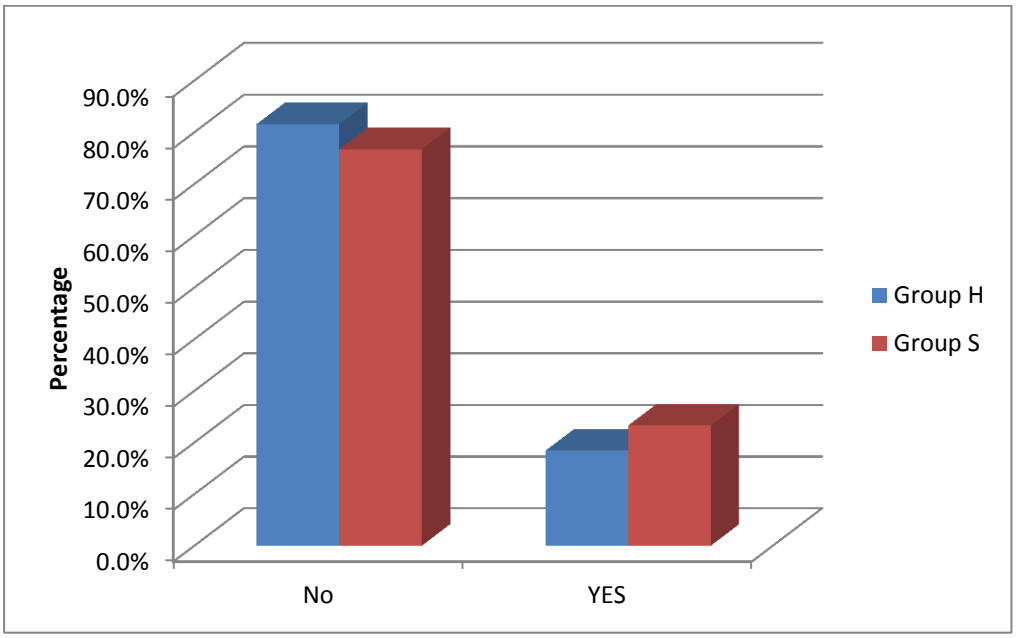


Figure 9: Incidence of Pain before administering study drug

Table 3B: Incidence of pain 15 secs after starting propofol infusion-

		Group H		Group S		Total	Chi-square value	p-value
		No. of cases	% age	No. of cases	% age			
After 15 secs of starting Propofol infusion	Unable to quantify Pain (U)	0	0.0%	0	0.0%	0	50.009	0.001
	No	67	65.0%	17	16.5%	84		
	YES	36	35.0%	86	83.5%	122		
Total		103	100.0%	103	100.0%	206		

All the patients were able to quantify pain 15 secs after starting propofol infusion. In Group H, 35% of patients had pain at cannula site 15 secs after starting propofol infusion. While in Group S, 83.5% of patients had pain at cannula site 15 secs after staring propofol infusion. This difference was statistically significant among the two groups with p value being 0.001.

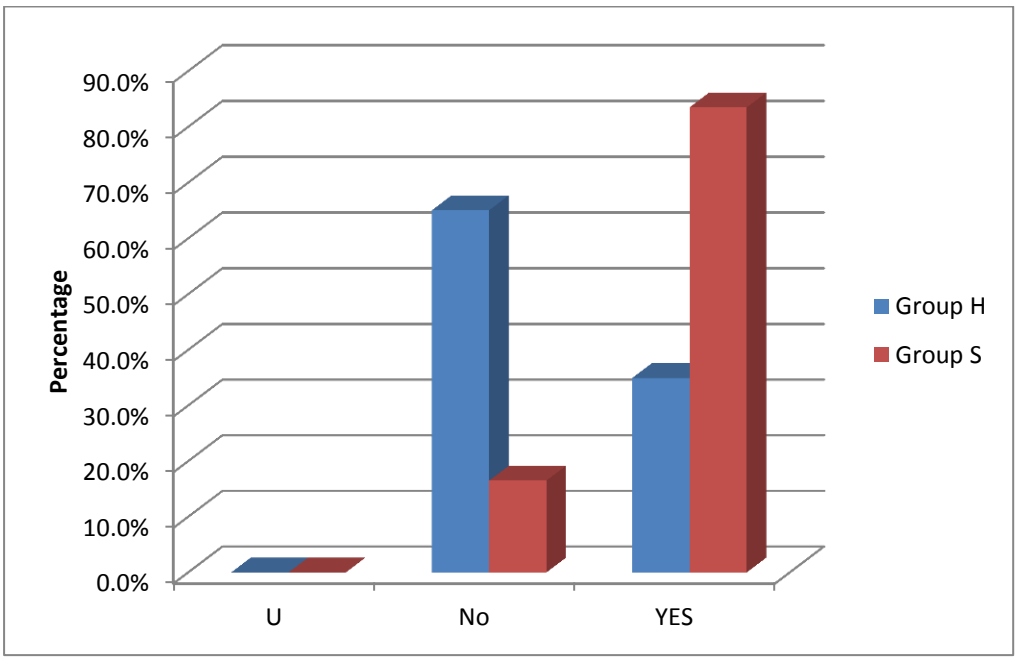


Figure 10: Incidence of Pain 15 secs after starting Propofol infusion

Table 3C: Incidence of pain 30 secs after starting propofol infusion

		Group H		Group S		Total	Chi-square value	p-value
		No. of cases	% age	No. of cases	% age			
After 30 secs of starting Propofol infusion	Unable to quantify pain (U)	0	0.0%	0	0.0%	0	59.266	0.001
	No	52	50.5%	3	2.9%	55		
	YES	51	49.5%	100	97.1%	151		
Total		103	100.0%	103	100.0%	206		

All the patients were able to quantify pain 30 secs after starting propofol infusion. In Group H, 49.5% of patients had pain at cannula site 30 secs after starting propofol infusion.

While in Group S, 97.1% of patients had pain at cannula site 30 secs after staring propofol infusion. This difference was statistically significant among the two groups with p value being 0.001.

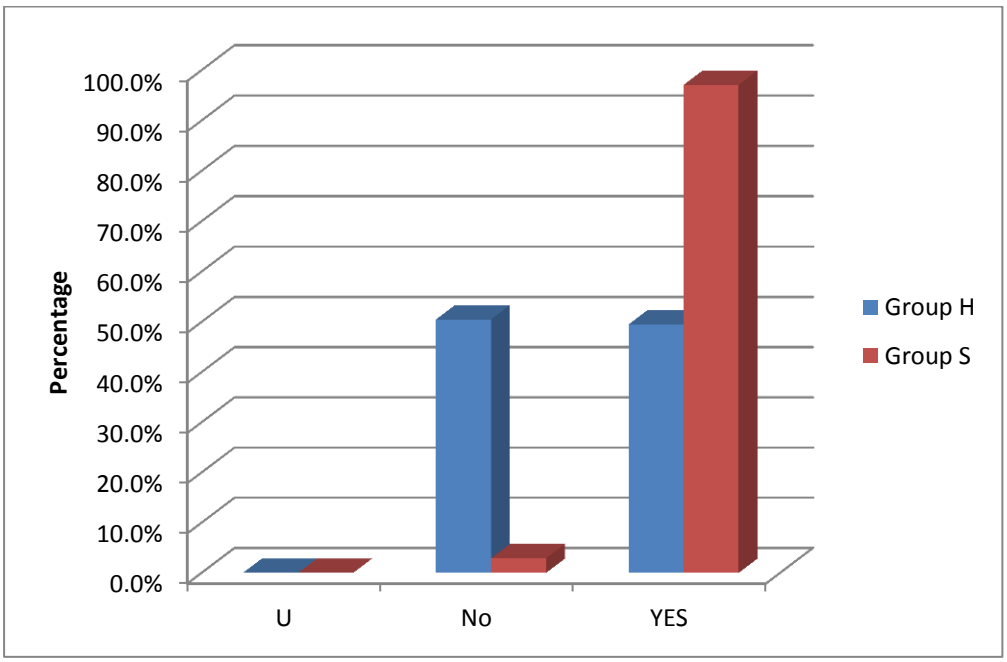


Figure 11: Incidence of Pain 30 secs after starting Propofol infusion

Table 3D: Incidence of pain 45 secs after starting propofol infusion

		Group H		Group S		Total	Chi-square value	p-value
		No. of cases	% age	No. of cases	% age			
After 45 Secs of starting Propofol infusion	Unable to quantify Pain(U)	9	8.7%	4	3.9%	13	47.049	0.001
	No	35	34.0%	0	0.0%	35		
	YES	59	57.3%	99	96.1%	158		
Total		103	100.0%	103	100.0%	206		

In Group H, 94 (out of 103) patients were able to quantify pain 45 secs after starting propofol infusion, out of which 59 patients had pain at cannula site and 35 patients had no pain at cannula site.

While in Group S, 99 (out of 103) patients were able to quantify pain 45 secs after starting propofol infusion out of which almost all patients (99 patients) had pain at cannula site. This difference was statistically significant among the two groups with p value being 0.001.

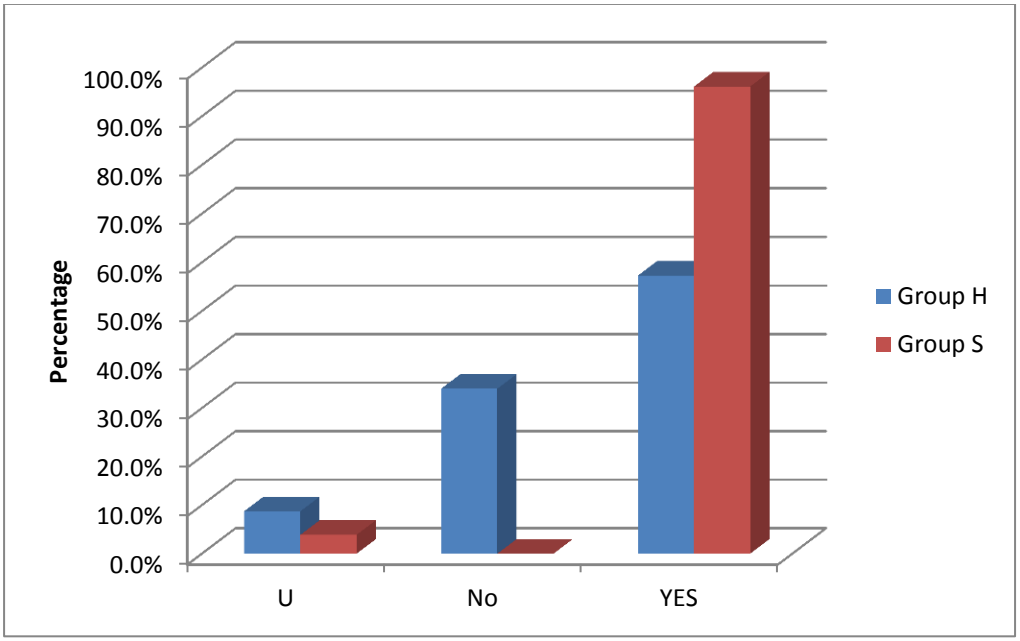


Figure 12: Incidence of Pain 45 secs after starting Propofol infusion

Table 3E: Incidence of pain 60 secs after starting propofol infusion-

		Group H		Group S		Total	Chi-square value	p-value
		No. of cases	% age	No. of cases	% age			
After 60 Secs of starting Propofol infusion	Unable to quantify Pain(U)	71	68.9%	75	72.8%	146	18.045	0.001
	No	16	15.5%	0	0.0%	16		
	YES	16	15.5%	28	27.2%	44		
Total		103	100.0%	103	100.0%	206		

In Group H, 32 of 103 patients were able to quantify pain 60 secs after starting propofol infusion out of which 16 patients had pain and 16 patients had no pain at cannula site.

While in Group S, 28 patients were able to quantify pain 60 secs after starting propofol infusion out of which almost all patients (28 patients) had pain at cannula site. This difference was statistically significant among the two groups with p value being 0.001.

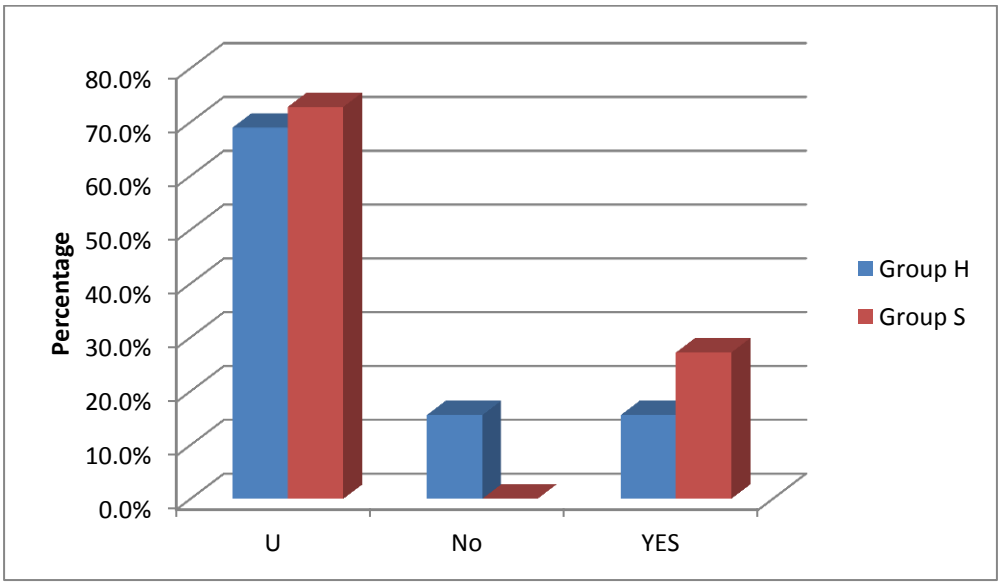


Figure 13: Incidence of Pain 60 secs after starting Propofol infusion

Table 4- NRS for pain at cannula site-

	Group H		Group S		Z	p-value
	Mean	SD	Mean	SD		
BEFORE	0.18	0.39	0.25	0.48	-0.917	0.359
AFTER 15 SECS	0.39	0.58	2.12	1.46	-9.024	0.001
30 SECS	0.72	0.91	3.23	1.25	-10.987	0.001
45 SECS	0.91	0.94	3.53	1.27	-10.700	0.001
60 SECS	0.59	0.67	3.57	1.20	-6.435	0.001

A-Before giving study drug-

The mean NRS for pain at cannula site before giving study drug for Group H was 0.18 ± 0.39. Similarly for Group S it was 0.25 ± 0.48.The difference of NRS between both groups was statistically not significant with p value being 0.359.

B- After 15 secs of starting propofol infusion-

The mean NRS for pain at cannula site 15 secs after starting propofol for Group H was 0.39 ± 0.58. Similarly for Group S it was 2.12 ± 1.46 .The difference of NRS between both groups was statistically significant with p value being 0.001.

C-After 30 secs of starting propofol infusion-

The mean NRS for pain at cannula site 30 secs after starting propofol for Group H was 0.72 ± 0.91. Similarly for Group S it was 3.23 ± 1.25 .The difference of NRS between both groups was statistically significant with p value being 0.001.

D- After 45 secs of starting propofol infusion-

The mean NRS for pain at cannula site 45 secs after starting propofol for Group H was 0.91 ± 0.94. Similarly for Group S it was 3.53 ± 1.27 .The difference of NRS between both groups was statistically significant with p value being 0.001.

E- After 60 secs of starting propofol infusion-

The mean NRS for pain at cannula site 60 secs after starting propofol for Group H was 0.59 ± 0.67. Similarly for Group S it was 3.57 ± 1.20.The difference of NRS between both groups was statistically significant with p value being 0.001.

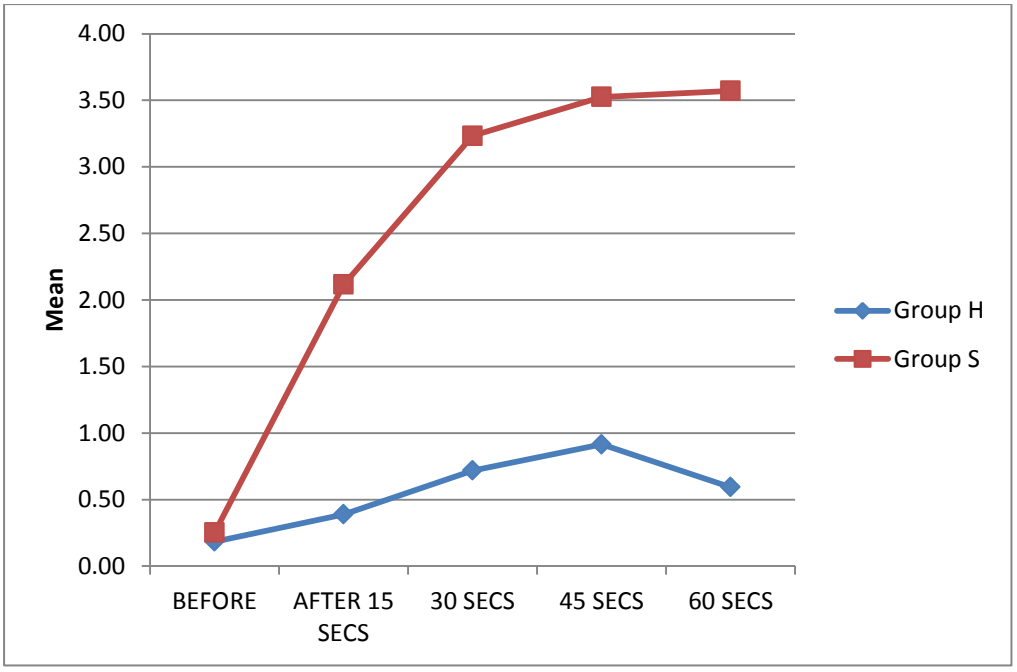


Figure 14: NRS for pain at cannula site

TABLE 5-Severity of Pain-

Table 5A: Severity of pain at cannula site before administering study drug

		Group H		Group S		Total	Chi-square value	p-value
		No. of cases	%age	No. of cases	%age			
Before Giving Study Drug	No	84	81.6%	79	76.7%	163	0.735	0.391
	Mild	19	18.4%	24	23.3%	43		
	Moderate	0	0.0%	0	0.0%	0		
	Severe	0	0.0%	0	0.0%	0		
Total		103	100.0%	103	100.0%	206		

In Group H, 81.6% of patients had no pain before giving the study drug whereas in Group S, 76.7% of patients had no pain before giving the study drug.

In Group H, 18.4% of patients had mild pain before giving the study drug whereas in Group S, 23.3% of patients had mild pain before giving the study drug.

In both groups, none of the patients had moderate to severe pain.

Both the groups were statistically comparable with respect to severity of pain at cannula site before administering the study drug. (p value-0.391).

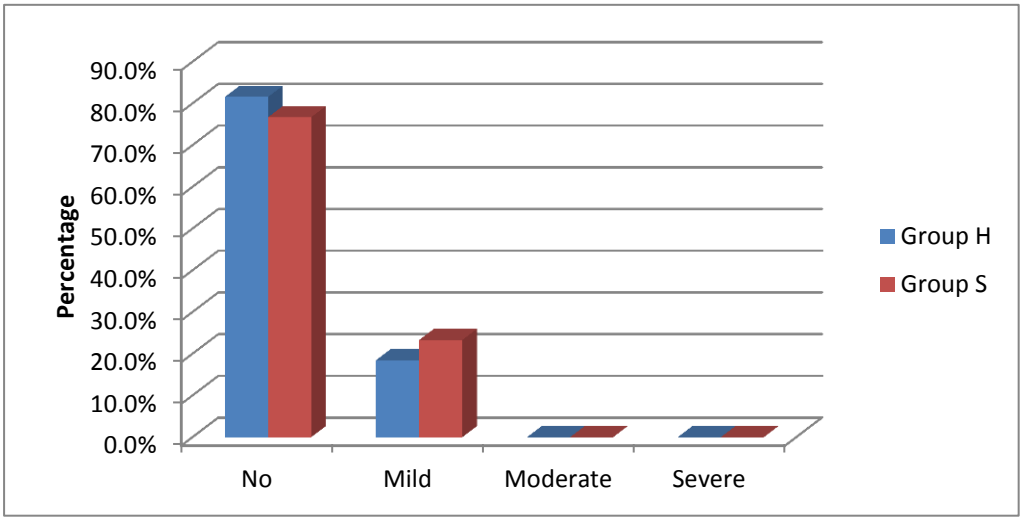


Figure 15: Severity of Pain before administering study drug

Table 5B: Severity of pain 15 secs after starting propofol infusion

		Group H		Group S		Total	Chi-square value	p-value
		No. of Cases	%age	No. of cases	%age			
After 15 Secs Of starting propofol infusion	Unable to quantify pain (U)	0	0.0%	0	0.0%	0	59.089	0.001
	No	67	65.0%	17	16.5%	84		
	Mild	36	35.0%	65	63.1%	101		
	Moderate	0	0.0%	21	20.4%	21		
	Severe	0	0.0%	0	0.0%	0		
Total		103	100.0%	103	100.0%	206		

All the patients in both the groups were able to quantify pain 15 secs after starting propofol infusion.

In Group H, 67 patients (65%) had no pain while 36 patients (35%) had mild pain. None of the patients had moderate to severe pain.

Whereas in Group S, 17 patients (16.5%) patients had no pain, 65 patients (63.1%) had mild pain, 21 patients (20.4%) had moderate pain and no patient had severe pain.

This difference was statistically significant among the two groups with p value being 0.001.

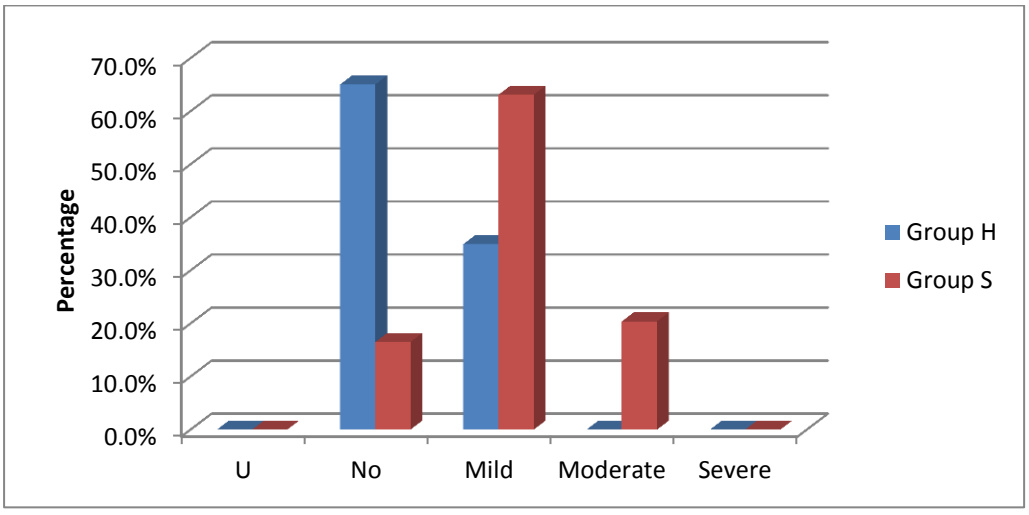


Figure 16: Severity of pain 15 secs after starting propofol infusion

Table 5C: Severity of pain 30 secs after starting propofol infusion

		Group H		Group S		Total	Chi-square value	p-value
		No. of cases	% age	No. of cases	% age			
After 30 secs of starting Propofol infusion	Unable to quantify pain (U)	0	0.0%	0	0.0%	0	81.661	0.001
	No	52	50.5%	3	2.9%	55		
	Mild	50	48.5%	60	58.3%	110		
	Moderate	1	1.0%	40	38.8%	41		
	Severe	0	0.0%	0	0.0%	0		
Total		103	100.0%	103	100.0%	206		

All the patients were able to quantify pain 30 secs after starting propofol infusion.

In Group H, 52 patients (50.5%) had no pain, 50 patients (48.5%) had mild pain, 1 patient (1%) had moderate pain while no patient had severe pain 30 secs after starting propofol infusion.

Whereas in Group S, 3 patients (2.9%) had no pain, 60 patients (58.3%) had mild pain, 40 patients (38.8%) had moderate pain and no patient had severe pain 30 secs after starting propofol infusion.

This difference was statistically significant among the two groups with p value being 0.001.

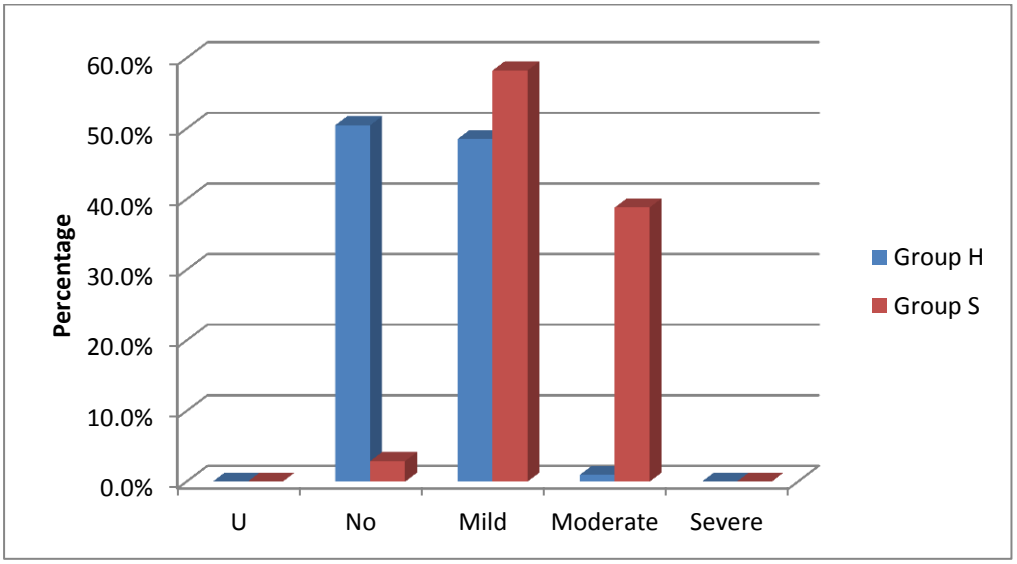


Figure 17: Severity of pain 30 secs after starting propofol infusion

Table 5D: Severity of pain 45 secs after starting propofol infusion

		Group H		Group S		Total	Chi-square value	p-value
		No. of cases	% age	No. of cases	% age			
After 45 Secs of Starting Propofol Infusion	Unable to quantify Pain	9	8.7%	4	3.9%	13	84.758	0.001
	No	35	34.0%	0	0.0%	35		
	Mild	58	56.3%	49	47.6%	107		
	Moderate	1	1.0%	50	48.5%	51		
	Severe	0	0.0%	0	0.0%	0		
Total		103	100.0%	103	100.0%	206		

In Group H, 94 patients were able to quantify pain 45 secs after starting propofol infusion. Out of total patients in Group H, 35 patients (34%) had no pain, 58 patients (56.3%) had mild pain, 1 patient (1%) had moderate pain and none of the patients had severe pain 45 secs after starting propofol infusion. However, 9 patients (8.7%) in Group H were unable to quantify pain as they lost their verbal response.

Whereas in Group S, 99 patients were able to quantify pain 45 secs after starting propofol infusion. Out of total patients in Group S, 49 patients (47.6%) had mild pain, 50 patients (48.5%) had moderate pain while no patient had severe pain 45 secs after starting propofol infusion. Four patients (3.9%) in Group S were unable to quantify pain 45 secs after starting propofol infusion.

This difference was statistically significant among the two groups with p value being 0.001.

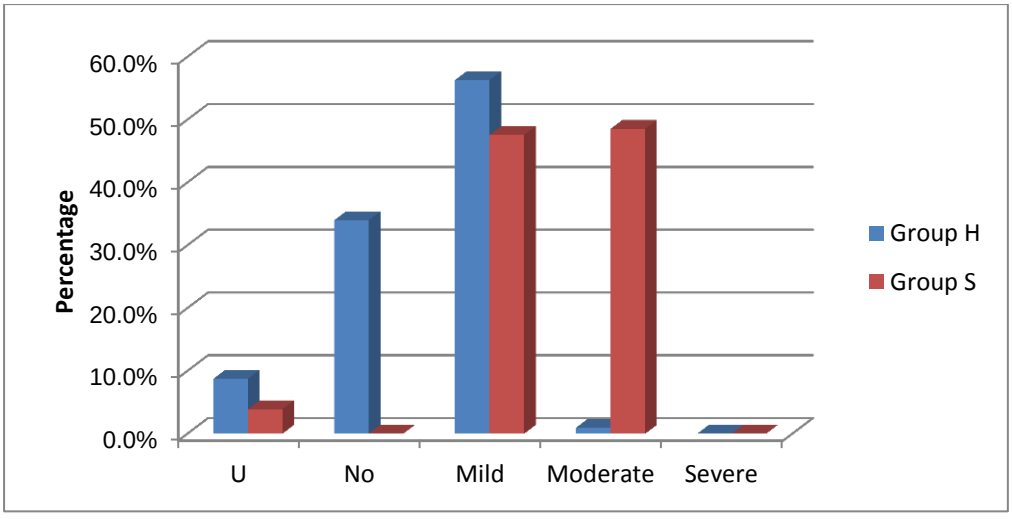


Figure 18: Severity of pain 45 secs after starting propofol infusion

Table 5E: Severity of pain 60 secs after starting propofol infusion

		Group H		Group S		Total	Chi-square value	p-value
		No. of cases	% age	No. of cases	% age			
After 60 Secs of Starting Propofol Infusion	Unable to quantify pain(U)	71	68.9%	75	72.8%	146	34.035	0.001
	No	16	15.5%	0	0.0%	16		
	Mild	16	15.5%	11	10.7%	27		
	Moderate	0	0.0%	17	16.5%	17		
	Severe	0	0.0%	0	0.0%	0		
Total		103	100.0%	103	100.0%	206		

In Group H, 32 patients were able to quantify pain 60 secs after starting propofol out of which 16 patients had no pain, 16 patients had mild pain and none of the patients had moderate to severe pain. However, 71 patients were unable to quantify pain 60 secs after starting propofol.

Whereas in Group S, 28 patients were able to quantify pain 60 secs after starting propofol out of which 11 patients had mild pain, 17 patients had moderate pain and none of the patients had severe pain. However 71 patients were not able to quantify pain 60 secs after starting propofol infusion.

This difference was statistically significant among the two groups with p value being 0.001.

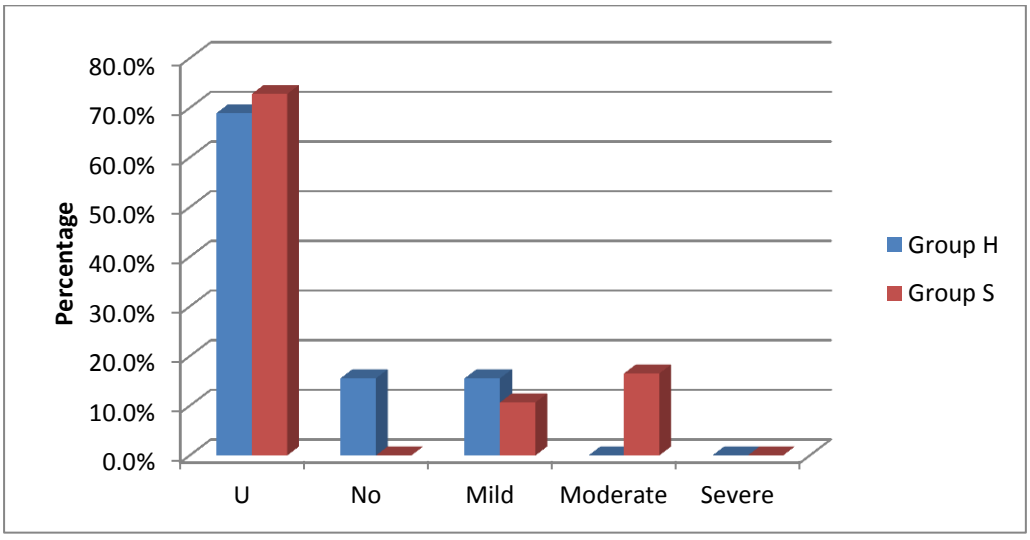


Figure 19: Severity of pain 60 secs after starting propofol infusion

Table 6: Mean Propofol duration (secs)

	Group H		Group S		Z	p-value
	Mean	SD	Mean	SD		
PROPOFOL DURATION (secs)	27.81	4.86	28.54	4.50	-0.607	0.544

The mean duration of propofol administration in Group H was 27.81 ± 4.86 secs and in Group S was 28.54 ± 4.50 secs. Both the groups were statistically comparable with respect to duration of propofol administration (p value- 0.544).

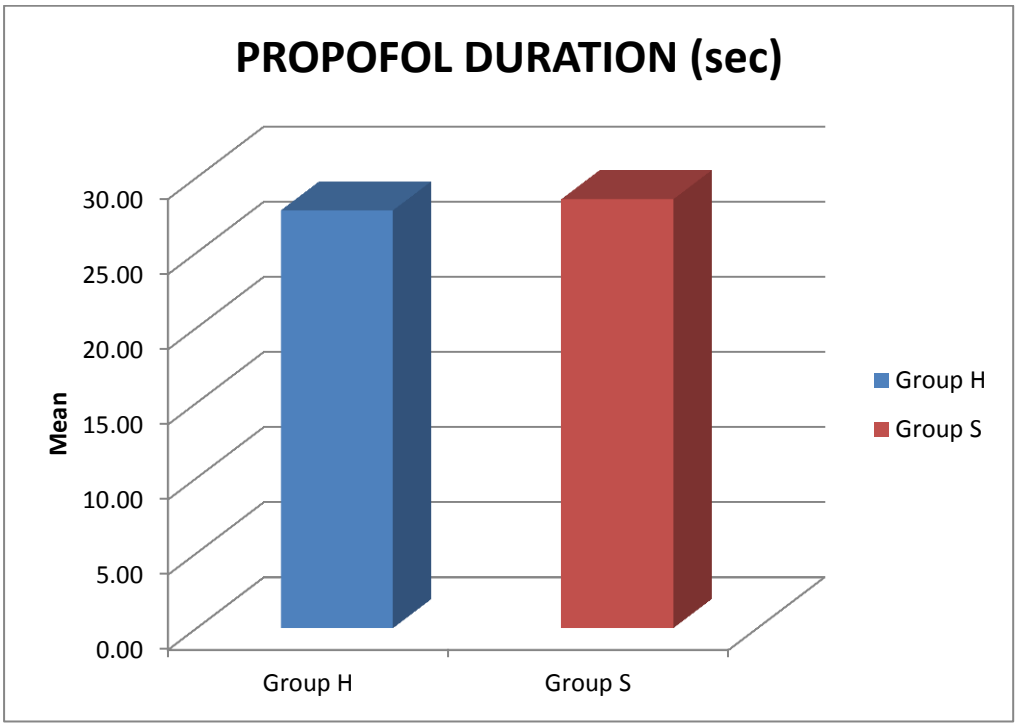


Figure 20: Mean duration of Propofol administration

DISCUSSION

Propofol is the preferred IV drug for both inducing and maintaining anaesthesia. Despite its close approximation to being the ideal IV anaesthetic, concerns persist regarding discomfort during its administration. While this discomfort is generally not regarded as a serious anaesthesia complication, some patients recall induction as the most painful aspect of the perioperative period, with reported pain incidence on limbs ranging from 30% to 90%.[14]

Several drugs are employed to alleviate propofol injection pain; however, pain incidence persists. After a comprehensive review of existing studies by Desuosa et al, it was concluded that a multimodal approach is optimal for managing propofol injection pain. They observed that using a single drug to reduce pain of propofol injection resulted in markedly greater incidence of pain as compared to pain on employing two drugs.[14] Many studies examining the effectiveness of different drugs in alleviating propofol injection pain have utilized high doses of anaesthetic and analgesic drugs. The increased concentration of these drugs may lead to undesirable side effects such as hypotension, which could potentially outweigh the discomfort caused by propofol injection.

A study by Jalota et al in 2011 investigated the efficacy of various methods, including lignocaine administration, in reducing pain associated with propofol injection. They found that while lignocaine significantly reduced the incidence of pain compared to control groups, some patients still experienced discomfort or pain during propofol injection.[76]

Colloids are used in anaesthesia for intraoperative fluid therapy [79] and are generally safe.[80] They are large molecules that can affect endothelial cell junctions and vascular permeability, and they inhibit endothelial activation by various substances. This action suggests that administering colloids beforehand might prevent propofol-induced contact activation, potentially reducing injection pain.[77, 81]

The administration of 6% HES, a colloid can potentially reduce the requirement for higher doses of anaesthetic and analgesic agents to manage propofol-induced pain. This approach presents an opportunity to minimize the use of opioids for pain reduction during propofol injection in patients, particularly those undergoing short surgical day care procedures. [30] Additionally, when combined with 2% lignocaine, HES may contribute further to lower the incidence of pain associated with propofol administration.

The purpose of this prospective, randomized study was to determine the role of 6% HES along with lignocaine in comparison to 0.9% saline with lignocaine for reducing the incidence and severity of pain of propofol injection.

There is a dearth of literature regarding the role of pre emptive HES administration for propofol injection pain. Only two studies regarding the use of 6% HES to decrease propofol induced pain have been found after a thorough research of literature.

In our study, we recruited 206 patients and divided them into two groups. Group H were administered total 50 ml of HES along with 2% lignocaine (1mg/kg) and Group S were administered total 50 ml of 0.9% saline along with 2% lignocaine over two minutes before induction with 1% propofol. Pain was assessed using NRS scale every 15 secs during administration of propofol till loss of verbal response. All the patients enrolled completed the study.

Prasad and Misra et al administered a greater volume i.e.100 ml of HES or normal saline over 3-5 minutes just before induction with propofol which was premixed with 2% lignocaine and they assessed pain using 3-point Likert Scale every 10 secs. Prasad included 100 patients, while Misra et al included 128 patients in their respective studies.[29, 30] A larger sample size in our study could potentially yield more robust and reliable data concerning the efficacy of HES in managing propofol-induced pain.

The demographic distribution in our study revealed that the patients in both the groups were comparable with respect to age, weight, BMI, gender, ASA physical status and the duration of propofol infusion.

Thus, there was uniformity of demographic profile in both groups which ensured that there were no confounding factors in the study.

Our primary objective was to measure the incidence of pain at 15, 30, 45, 60 secs after starting propofol infusion till loss of verbal response. It was observed that pain at cannula site before administration of study drugs was insignificant in both the groups.

Incidence of pain 15 secs after starting propofol in Group H was less as compared to Group S (35% vs 83.5%) . After 30 secs of starting propofol administration, incidence of pain was 49.5% in Group H as compared to 97.1% in Group S.

In Group H, 94 patients and in Group S, 99 patients were able to quantify pain at 45 secs. After 45 secs of starting propofol, 57.3% of total patients in Group H had pain while 96.1% of total patients in Group S had pain at cannula site.

After 60 secs of starting propofol infusion, only 32 patients were able to quantify pain in Group H out of which half patients had pain while in Group S, 28 patients were able to quantify pain and all of them had pain at the cannula site. Incidence of pain was significantly less at all observation intervals in Group H (p value- 0.001). Our findings are in coherence with the findings of Prasad as their incidence of discomfort was also considerably greater in the NS group compared to HES group (50% vs 30%). Similar results are evident from the study by Misra et al where the incidence of pain was significantly higher in the NS group compared to HES group (53% vs 28%) as found in our study. On the basis of above findings, we can suggest that a combination of 6% HES with 2% lignocaine may be better than control group of 0.9% Saline with 2% lignocaine in preventing propofol injection pain.

It is important to note that we administered lignocaine separately from the study drug and did not mix it with propofol. In contrast, Prasad and Misra et al. mixed lignocaine directly with propofol. According to previous literature, mixing propofol with lignocaine can potentially cause oil droplet coalescence, which increases the risk of pulmonary embolism. [24] Additionally, Reddy et al. reported instability of the propofol-lignocaine emulsion, especially with higher doses of

lignocaine or if there is a delay between preparation and administration. [25]

We used NRS scale for rating pain instead of Likert Scale used by Prasad and Misra. This decision was motivated by concerns that the Likert Scale might lead to potential overlaps in the severity ratings of pain. Severity of pain was assessed using NRS scale by grading them into mild, moderate and severe.

NRS used for pain assessment was comparable in both the groups before giving study drug (0.18 ± 0.39 in Group H vs. 0.25 ± 0.48 in Group S). After starting propofol infusion, patients in Group S reported more pain at all observation intervals i.e. 15,30,45,60 secs with mean NRS being 2.12 ± 1.46, 3.23 ± 1.25, 3.53 ± 1.27, 3.57 ± 1.20 respectively as compared to Group H, where mean NRS was 0.39 ± 0.58, 0.72 ± 0.91, 0.91 ± 0.94, 0.59 ± 0.67 respectively at same observation intervals. This pain difference was statistically significant among both groups with Group H reporting less pain at all observation intervals with p value being 0.001.

Both groups were comparable with respect to pain before administration of study drug. After 15 secs of starting propofol infusion, the incidence of moderate pain was higher in Group S as compared to Group H (20.4% vs 0%). The incidence of mild pain was more in Group S as compared to Group H (63.1% vs 35%). However, the overall pain score was significantly less in Group H as compared to Group S at 15 secs with p value being 0.001.

After 30 secs of starting propofol infusion, the incidence of moderate pain was higher in Group S as compared to Group H (38.8% vs 1%). The incidence of mild pain was also more in Group S as compared to Group H (58.3% vs 48.5%). Overall, the pain score was significantly less in Group H as compared to Group S (p value-0.001).

After 45 secs of starting propofol infusion, 94 patients in Group H and 99 patients in Group S were able to quantify pain. Out of total patients in Group H, 34% were pain free, 56.3% had mild pain and 1% had moderate pain. While out of total patients in Group S, none of the patient was pain free, 47.6% had mild pain and 48.5% had moderate

pain. Overall, the pain was statistically significant in both groups with pain being lesser in Group H.

After 60 secs of starting propofol infusion, 32 patients in Group H and 28 patients in Group S were able to quantify pain. Out of total patients in Group H, 16% were pain free, 16% had mild pain and none of them had moderate pain. While out of total patients in Group S, none of the patient was pain free, 10.7% had mild pain and 16.5% had moderate pain Overall, the pain was significantly less in Group H with p value being 0.001. In our study, none of the patients in both groups reported severe pain after starting of propofol infusion.

Our findings are much in line with those observed by Prasad where the incidence of severe pain was greater in the NS group as compared to HES group (6% vs 0%), and the incidence of moderate pain was also higher in the NS group (14% vs 6%), while the incidence of mild pain was more or less equivalent (30% vs 24%; NS vs HES). Between the two groups, there was a significant difference in terms of the level of pain experienced.[29] Similar results were found by Mishra et al where the incidence of severe (8% vs 0%) and moderate pain (16% vs 5%) was higher in the NS group, while the incidence of mild pain was comparable (29% vs 23%) in NS vs HES groups.[30]

As propofol (2mg/kg) was administered at constant rate of 0.5ml/sec, the mean duration of administration of propofol was comparable in both the groups.

All the above findings strongly support the efficacy of HES with lignocaine over 0.9% Saline with lignocaine for prevention of propofol induced pain.

The findings of our study are in concordance with the interpretations from studies from Prashad and Mishra with respect to incidence and severity of pain. Based on our observations, we suggest better role of HES to mitigate propofol injection pain in comparison to normal saline.

A certain limitations of our study are worth mentioning-

There was early induction of anaesthesia in some patients (loss of verbal response) as some patients were unable to quantify pain at 45 and 60 secs which might affect the pain score in both groups.

We used Numeric Rating Scale to quantify pain, but this pain score is contingent upon individual perception, highlighting the need for an observational scale to ensure precise assessment of pain. However, NRS is better than likert Scale used by Prasad and Misra et al.

We used 6% HES in our study, so the results of study may not be applicable to other starches. Thus, the need of the hour is further studies using other starches to compare their efficacy in reducing propofol injection pain.

Although our study had its limitations, it also provided several advantages. We standardized the size and placement of the cannula, ensuring consistency across all participants. Additionally, we used a single brand of propofol throughout the study to maintain uniformity. The infusion rate of propofol was strictly controlled for each patient. Moreover, we opted for the NRS instead of the Likert scale for pain assessment, as it is known for its enhanced accuracy in measuring pain intensity. These measures collectively strengthened the reliability and precision of our study findings.

We thus conclude from the results of our study that IV HES with lignocaine is more effective than 0.9% saline with lignocaine in reducing propofol induced pain. The use of HES prior to administration of propofol can significantly enhance patient’s satisfaction and comfort during anaesthesia induction, contributing to a smoother and more comfortable experience.

SUMMARY AND CONCLUSION

The present study was conducted in the Department of Anaesthesia, Dayanand Medical College and Hospital, Ludhiana after approval from Institutional Ethics Committee. A total of 206 ASA I and II patients, aged between 18 and 65 yrs, scheduled for elective surgeries under general anaesthesia, were enrolled in this prospective, double blind, randomized controlled trial. Patients were randomly allotted to two groups of 103 patients each.

Group H patients were administered a total bolus of 50ml of 6% HES with 2% lignocaine (1mg/kg) IV.

Group S patients were administered a total bolus of 50ml of 0.9% saline with 2% lignocaine (1mg/kg) IV.

The study drug was administered over a period of two mins before starting induction with 1% propofol infusion at the rate of 0.5 ml/sec. Pain on the IV cannula site after starting propofol was assessed using NRS every 15 secs until the loss of verbal response. The incidence and severity (mild, moderate, severe) of pain were noted in both the groups.

The technique of general anaesthesia was standardized in both groups.

The following conclusions were drawn during the study period:

- Both groups were comparable with respect to the demographic data, ASA physical status and duration of propofol administration.
- The incidence of pain was significantly reduced in Group H at 15,30,45,60 secs (35%, 49.5%, 57.3%,15.5% respectively) compared to Group S
  (83.5%, 97.1%, 96.1%, 27.2% at the same observation intervals) (p value 0.001).
- The NRS score was also significantly reduced in Group H at 15,30,45,60 secs (0.39 ± 0.58, 0.72 ± 0.91, 0.91 ± 0.94, 0.59 ± 0.67) compared to Group S (2.12 ± 1.46, 3.23 ± 1.25, 3.53 ±

1.27, 3.57 ± 1.20) at the same observation intervals (p value 0.001).

- At 15 secs after starting propofol infusion, the incidence of mild pain in Group S was greater than in Group H (63.1% vs 35%). The incidence of moderate pain was also higher in Group S compared to Group H (20.4% vs 0%). Overall, the pain was significantly less in Group H comapared to Group S (p value 0.001).
- At 30 secs after starting propofol infusion, the incidence of mild pain in Group S was greater than in Group H (58.3% vs 48.5%). The incidence of moderate pain was also higher in Group S compared to Group H (38.8% vs 1%). Overall, pain was significantly less in Group H comapared to Group S (p value 0.001).
- At 45 secs after initiating propofol infusion, Group S exhibited a higher incidence of moderate pain compared to Group H (48.5% vs. 1%). Group H, conversely, showed a higher incidence of mild pain compared to Group S (56.3% vs. 47.6%). Overall, Group H experienced significantly less pain compared to Group S (p = 0.001).
- At 60 secs following the commencement of propofol infusion, Group S exhibited a higher incidence of moderate pain compared to Group H (16.5% vs. 0%). Conversely, Group H had a higher incidence of mild pain compared to Group S (15.5% vs. 10.7%). Overall, Group H experienced significantly less pain than Group S (p = 0.001).
- None of the patients in either group experienced severe pain.

The above findings suggest that IV 6% HES along with 2% lignocaine is more effective than 0.9% saline with 2% lignocaine in reducing pain following propofol injection.

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KEY TO MASTER CHART

MRD- Medical Records Department

No- Number

yrs- years

M- Male

F- Female

Kg- Kilogram

BMI- Body Mass Index

Kg/m2- Kilogram/meter^2

ASA- American Society of Anaesthesiologists

bpm- Beats per minute

SBP- Systolic Blood Pressure

mmHg- millimetres of mercury

DBP- Diastolic Blood Pressure

SpO2- Peripheral oxygen saturation

% - Percentage

secs- seconds

S.NO.	Randomization	MRD NO	PATIENT INITIALS	AGE (yrs)	GENDER	WEIGHT (kg)	BMI (kg/m2)	ASA	SURGERY PLANNED	DRUG ALLERGY	HEART RATE (/min)	SBP (mm Hg)	DBP (mm Hg)	SPO2 (%)	PROPOFOL START TIME	PROPOFOL FINISH TIME	PROPOFOL ADMINISTRATION DURATION (secs)	PAIN SCORE BEFORE Study Drug	PAIN SCORE FOLLOWING PROPOFOL ADMINISTRATION			
																			AFTER 15 SECS	AFTER 30 SECS	AFTER 45 SECS	AFTER 60 SECS
1	S	1476889	PL	57	M	60	17.9	I	SEPTOTURBINOPLASTY	-	96	110	80	98	08:32:05	08:32:28	23	0	0	0	2	2
2	S	1463712	HK	40	F	68	24.9	II	RIGHT SUPERFICIAL PAROTIDECTOMY	CEPHALOSPORINS	68	114	72	98	09:00:15	09:00:42	27	1	1	2	2	-
3	H	1465477	RR	34	F	73	26	I	LAPROSCOPIC CHOLECSTECTOMY	-	92	128	92	99	12:15:04	12:15:33	29	0	0	0	0	1
4	S	1317740	JK	26	F	54	21.1	I	RIGHT REVISION TYMPANOPLASTY	-	84	128	70	99	12:34:08	12:34:29	21	0	2	3	3	-
5	S	1457722	KK	32	F	60	23.4	I	MYOMECTOMY	-	84	114	70	98	01:04:50	01:05:14	24	0	1	4	5	6
6	H	1462715	A	22	F	54	19.8	I	LAPROSCOPIC CHOLECSTECTOMY	-	82	110	80	99	09:15:04	09:15:25	21	0	0	0	0	0
7	H	1464925	IB	19	F	56	20.5	I	SEPTOTURBINOPLASTY	-	70	108	68	99	09:48:05	09:48:27	22	0	0	0	1	-
8	S	1461735	SS	40	M	84	30.8	II	PANFACIAL FRACTURE	-	94	140	92	97	10:15:45	10:16:17	32	0	1	2	2	-
9	H	1449066	GS	32	M	87	28.3	I	SEPTOTURBINOPLASTY	-	80	128	92	98	12:08:10	12:08:44	34	0	0	1	1	0
10	H	830335	RS	24	M	60	21.3	I	CYSTOSCOPY	STREPTOMYCIN,DIARY PRODUCTS	98	114	72	99	02:02:10	02:02:34	24	0	0	0	1	0
11	S	1463696	DS	32	M	64	23	I	SEPTOTURBINOPLASTY	-	68	130	92	98	08:55:50	08:56:15	25	0	1	2	2	-
12	H	1453082	CK	27	F	38	14.8	I	MICROLARYNGEAL SURGERY	-	98	120	70	98	10:15:15	10:15:31	16	0	0	0	0	0
13	S	1463289	K	25	F	60	24.2	I	LAPROSCOPIC CHOLECSTECTOMY	-	84	122	84	98	12:10:45	12:11:09	24	0	2	3	4	4
14	H	1447365	NS	18	F	43.9	18.9	I	INCISION AND DRAINAGE	-	92	114	70	99	03:05:10	03:05:27	17	0	0	0	1	1
15	H	1462715	A	22	M	54	20.4	I	LAPROSCOPIC CHOLECSTECTOMY	-	110	128	70	98	09:45:08	09:45:29	21	0	0	0	0	0
16	H	1464925	IB	19	F	46	18.5	I	SEPTORHINOPLASTY	-	100	112	70	99	09:52:08	09:52:26	18	0	0	0	0	1
17	H	1440475	P	27	F	54	21.8	II	LAPROSCOPIC CHOLECSTECTOMY	-	94	110	60	98	11:10:08	11:10:30	22	0	1	0	0	-
18	S	1438556	AK	35	M	74	27	II	WIDE EXCISION TONGUE	-	64	130	92	98	01:45:10	01:45:40	30	0	1	2	3	-
19	H	1474803	SK	57	M	84	29.9	II	SEPTOTURBINOPLASTY	-	89	130	80	99	02:08:40	02:09:13	33	0	1	1	0	0
20	S	1468574	KK	37	F	64	24.2	I	LAPROSCOPIC CHOLECSTECTOMY	-	80	130	72	99	09:45:15	09:45:40	25	0	2	3	3	-
21	H	1479110	MH	24	M	77	28.3	II	NASAL BONE REDUCTION	-	90	110	80	97	11:38:40	11:39:10	30	1	1	1	1	1
22	H	1387856	BB	21	M	61.8	19.6	II	STOMA CLOSURE	-	88	112	72	99	01:40:24	01:40:48	24	0	0	0	0	0
23	S	1443472	A	28	M	70	22.8	I	FUNCTIONAL ENDOSCOPIC SINUS SURGERY	-	84	120	70	98	03:01:18	03:01:46	28	1	1	3	3	4
24	S	8992	JK	47	F	81	30.7	I	LAPROSCOPIC CHOLECSTECTOMY	-	82	124	80	99	09:48:20	09:48:52	32	0	1	2	2	-
25	S	1461833	K	29	F	62	23.5	II	ORIF WITH PLATING	-	82	112	70	98	11:46:25	11:46:50	25	0	2	2	3	-
26	S	275294	NK	23	F	46	18.5	I	LABIAL CYST EXCISION	-	90	114	70	99	02:10:40	02:10:58	18	0	2	3	3	-
27	H	1482365	SJ	46	F	86	32.7	II	LAPROSCOPIC CHOLECYSTECTOMY	-	94	140	82	98	09:50:24	09:50:58	34	0	0	1	0	0
28	H	1468867	BS	60	M	87	29.9	I	OPEN MESH HERNIOPLASTY	-	83	116	74	98	11:40:25	11:40:59	34	0	1	1	0	0
29	H	1479931	KM	30	F	60	25	I	UMBILICAL HERNIA REPAIR	-	66	110	70	98	01:15:06	01:15:30	24	1	1	2	1	-
30	H	1170217	SK	56	F	80	31.2	II	LAPROSCOPIC CHOLECYSTECTOMY	-	72	120	80	98	03:01:48	03:02:20	32	0	0	1	0	0
31	S	1436887	RA	34	F	71	27.7	II	BREAST MASS EXCISION	-	80	110	62	98	09:46:05	09:46:33	28	1	2	3	3	2
32	S	1485891	JS	32	M	84	26.6	II	LIPOSUCTION	-	86	110	70	98	01:24:02	01:24:35	33	0	2	4	4	3
33	S	1487023	HK	65	F	62	26	II	LAPROSCOPIC CHOLECYSTECTOMY	-	69	130	80	97	10:49:06	10:49:31	25	0	0	2	2	-
34	H	1487275	PR	44	F	80	30.3	II	HYSTERECTOMY	-	70	138	78	98	01:35:15	01:35:47	32	0	1	1	0	1
35	H	1489005	PS	58	M	65	25.4	II	LAMINECTOMY	TERBINAFINE	84	120	70	97	03:01:40	03:02:16	36	0	1	1	1	1
36	S	1488595	MR	24	F	47	19	II	FEEDING JEJUNOSTOMY	-	70	100	60	98	09:35:04	09:35:23	19	0	3	3	2	-
37	S	1489355	HM	39	M	70	24.2	I	LAPROSCOPIC CHOLECYSTECTOMY	-	72	130	80	99	11:50:45	11:51:16	31	0	4	3	3	3
38	H	1489485	DS	59	M	65	24	I	LAPROSCOPIC CHOLECYSTECTOMY	-	80	130	80	99	02:15:51	02:16:17	26	0	1	1	0	0
39	S	1389805	BS	47	M	80	25.3	II	GASTROJEJUNOSTOMY	-	84	124	82	99	08:45:10	08:45:42	32	0	2	2	2	3
40	S	1545189	KS	43	M	60	25.2	II	LAPROSCOPIC CHOLECYSTECTOMY	-	68	130	82	99	10:02:00	10:02:24	24	0	2	3	3	-
41	S	1559303	MK	56	M	70	24.9	II	LAPROSCOPIC CHOLECYSTECTOMY	-	80	134	84	98	12:02:45	12:03:13	28	0	1	1	1	2
42	S	1401089	SS	36	M	79	29	I	LAPROSCOPIC CHOLECYSTECTOMY	-	66	130	70	100	01:15:40	01:16:11	31	0	2	2	3	3
43	H	1465477	RR	34	F	73	26	I	LAPROSCOPIC CHOLECYSTECTOMY	-	90	128	92	99	03:05:00	03:05:29	29	0	0	0	0	1
44	H	503138	SN	73	M	72	25.6	I	LAPROSCOPIC CHOLECYSTECTOMY	-	80	128	82	99	04:05:45	04:06:13	28	1	1	2	2	2

S.NO.	Randomization	MRD NO	PATIENT INITIALS	AGE (yrs)	GENDER	WEIGHT (kg)	BMI (kg/m2)	ASA	SURGERY PLANNED	DRUG ALLERGY	HEART RATE (/min)	SBP (mm Hg)	DBP (mm Hg)	SPO2 (%)	PROPOFOL START TIME	PROPOFOL FINISH TIME	PROPOFOL ADMINISTRATION DURATION (secs)	PAIN SCORE BEFORE Study Drug	PAIN SCORE FOLLOWING PROPOFOL ADMINISTRATION			
																			AFTER 15 SECS	AFTER 30 SECS	AFTER 45 SECS	AFTER 60 SECS
45	H	802484	JR	32	F	52	20.3	I	LAPROSCOPIC CYSTECTOMY	-	98	110	72	100	10:05:20	10:05:40	20	0	0	0	0	-
46	H	1494259	ES	19	M	77	29.1	I	MIDDLE MEATAL ANTROSTOMY	-	84	120	70	99	11:45:06	11:45:36	30	0	0	1	0	-
47	H	1452567	GS	27	M	74	22.1	I	STOMA CLOSURE	-	68	110	70	100	12:08:06	12:08:35	29	0	0	0	1	0
48	S	1550657	JK	53	F	60	23.4	II	LAPROSCOPIC CHOLECYSTECTOMY	-	84	118	70	99	03:05:45	03:06:09	24	1	2	4	4	-
49	S	1330443	NK	65	F	60	22.7	II	LAPROSCOPIC CHOLECYSTECTOMY	-	82	130	80	99	09:15:40	09:16:04	24	0	1	3	5	-
50	H	1546058	B	35	F	55	20.8	II	HYDATID CYST EXCISION	-	76	130	90	99	11:15:12	11:15:34	22	0	1	1	-	-
51	S	1552162	HS	23	M	74	26.3	I	LAPROSCOPIC CHOLECYSTECTOMY	-	66	134	72	99	12:45:10	12:45:39	29	0	2	3	4	4
52	S	1549350	JD	63	F	64	25	II	LAPROSCOPIC CHOLECYSTECTOMY	-	68	140	92	100	01:48:06	01:48:31	25	0	4	4	5	-
53	H	1552583	MA	46	F	70	24.9	II	LAPROSCOPIC CHOLECYSTECTOMY	-	82	118	82	100	03:05:04	03:05:32	28	0	0	0	0	0
54	H	1538815	MD	32	F	62	25	I	TYMPANOPLASTY	-	70	120	70	100	09:05:45	09:06:09	24	0	1	1	0	-
55	S	1550363	AD	62	F	64	24.2	II	LAPROSCOPIC CHOLECYSTECTOMY	-	68	138	86	99	10:48:05	10:48:30	25	0	1	3	3	-
56	H	1610472	PK	41	F	68	27	II	END AURAL TYMPANOPLASTY	-	90	128	70	99	12:05:08	12:05:35	27	0	0	0	1	-
57	H	1472653	KS	23	M	70	25.7	I	LAPROSCOPIC CHOLECYSTECTOMY	-	90	124	82	100	03:05:12	03:05:40	28	0	0	1	1	1
58	H	1208743	HK	30	F	78	27.8	I	POLYPECTOMY	DOXYCYCLINE	94	120	84	97	09:12:06	09:12:37	31	1	1	1	2	2
59	H	1555349	VK	35	M	70	24.2	I	FUNCTIONAL ENDOSCOPIC SINUS SURGERY	-	78	130	84	98	10:30:15	10:30:43	28	0	0	0	0	-
60	H	1553632	YH	65	M	90	29.3	II	LAPROSCOPIC CHOLECYSTECTOMY	-	90	140	70	97	11:12:48	11:13:24	36	0	0	1	1	0
61	H	1556227	A	37	F	60	23.4	II	LAPROSCOPIC CHOLECSYTECTOMY	-	70	114	72	98	12:05:45	12:06:09	24	0	0	1	0	-
62	S	469161	JK	18	F	65	25.4	I	SEPTORHINOPLASTY	-	98	114	70	97	03:15:42	03:16:08	26	2	5	5	6	-
63	S	1556681	PK	46	F	68	24.9	II	HYSTERECTOMY	-	70	128	84	98	09:48:40	09:49:07	27	1	3	3	4	-
64	H	1556451	SK	31	F	54	24.2	I	BILATERAL FESS	-	100	118	74	97	01:42:09	01:42:30	21	0	1	1	1	-
65	H	1557417	JS	53	M	70	24.9	II	STOMA CLOSURE	-	100	140	100	97	03:40:15	03:40:43	28	0	0	0	1	-
66	H	169272	SK	44	M	100	29.9	II	ORIF PELVIS AND SHOULDER	-	112	110	70	96	09:45:06	09:45:46	40	0	0	0	1	1
67	S	1616365	AS	31	M	72	24.9	I	FESS AND SEPTOPLASTY	-	84	104	68	99	12:05:08	12:05:36	28	0	3	4	4	4
68	S	1584414	MS	45	M	58	21.3	II	LAMINECTOMY	-	98	124	82	97	01:15:12	01:15:35	23	1	3	3	4	-
69	S	1598548	AKK	29	F	60	22	I	SEPTOPLASTY	-	70	110	70	98	08:50:09	08:50:33	24	0	1	3	4	-
70	S	1596320	N	21	M	74	27.1	I	SEPTOTURBINOPLASTY	-	80	128	72	97	10:05:07	10:05:36	29	0	2	2	3	4
71	H	1596325	YK	60	F	75	29.3	II	PARTOIDECTOMY	-	78	126	72	98	12:45:35	12:46:05	30	1	2	1	1	-
72	S	1601509	N	42	F	64	25	I	TYMPANOMASTOIDECTOMY	-	70	124	86	99	02:15:48	02:16:13	25	0	0	3	3	-
73	S	1616714	TPS	46	M	78	29.5	I	HAEMORRHOIDECTOMY	-	70	132	84	98	08:54:42	08:55:13	31	0	3	3	4	4
74	H	1609158	CK	60	F	72	29	II	HEMITHYROIDECTOMY	-	90	100	60	99	10:48:12	10:48:40	28	0	0	0	1	-
75	S	1620365	SD	60	F	72	27.2	II	DEBDRIDEMENT NECK WOUND	-	74	134	92	98	11:02:45	11:03:14	29	0	2	3	3	-
76	S	573575	GS	33	M	84	29	I	LAPROSCOPIC CHOLECYSTECTOMY	-	80	128	73	98	01:05:10	01:05:44	34	0	3	4	4	5
77	S	1617158	N	45	F	62	23.5	II	PAROTID ABSCESS INCISION AND DRAINAGE	-	86	128	72	98	04:05:02	04:05:27	25	0	2	3	3	-
78	H	1611316	DS	43	M	72	26	II	MICROLARYNGEAL SURGERY	-	70	130	84	100	09:48:40	09:49:09	29	0	0	0	0	0
79	S	1625575	IS	24	M	62	22.1	I	ORIF WITH PLATING	-	120	127	76	98	11:15:46	11:16:11	25	1	4	4	3	-
80	S	1323937	JS	41	M	78	26.9	I	LAPROSCOPIC CHOLECYSTECTOMY	-	78	128	86	98	01:48:15	01:48:46	31	0	0	1	1	1
81	H	1612750	MK	50	F	70	27	II	TIBIA PLATING	-	72	136	92	99	03:40:10	03:40:38	28	0	0	0	0	-
82	H	1609192	AK	36	F	60	22	I	LAPROSCOPIC CHOLECYSTECTOMY	-	80	128	86	98	08:48:15	08:48:39	24	0	0	0	0	-
83	S	1603146	V	23	M	72	25.6	I	COMMON PERONEAL N. EXPLORATION	-	100	110	62	98	09:40:15	09:40:43	28	0	0	2	3	-
84	S	1625645	AK	30	M	68	24.2	II	PACK REMOVAL AND PROCEED	-	88	140	84	97	02:45:05	02:45:32	27	0	2	3	3	-
85	S	1564350	VN	38	M	80	27.6	I	LIPOSUCTION	-	76	128	84	98	09:40:15	09:40:47	32	0	0	3	3	4
86	H	1625851	PS	26	M	70	24.2	I	LAPROSCOPIC CHOLECYSTECTOMY	-	85	126	84	98	12:45:15	12:45:42	27	1	1	2	2	-
87	S	679265	SS	57	M	68	23.5	II	CYSTOSCOPY	-	70	130	84	97	03:45:10	03:45:37	27	0	3	3	4	-

S.NO.	Randomization	MRD NO	PATIENT INITIALS	AGE (yrs)	GENDER	WEIGHT (kg)	BMI (kg/m2)	ASA	SURGERY PLANNED	DRUG ALLERGY	HEART RATE (/min)	SBP (mm Hg)	DBP (mm Hg)	SPO2 (%)	PROPOFOL START TIME	PROPOFOL FINISH TIME	PROPOFOL ADMINISTRATION DURATION (secs)	PAIN SCORE BEFORE Study Drug	PAIN SCORE FOLLOWING PROPOFOL ADMINISTRATION			
																			AFTER 15 SECS	AFTER 30 SECS	AFTER 45 SECS	AFTER 60 SECS
88	S	1616004	BR	62	F	68	25.7	II	LAPROSCOPIC CHOLECYSTECTOMY	-	70	140	92	98	09:48:10	09:48:37	27	0	2	3	3	-
89	S	1626245	S	48	F	68	24.9	II	BREAST LUMP EXCISION	-	68	132	80	98	12:45:15	12:45:42	27	1	5	6	5	-
90	H	1626306	JS	53	M	78	28.6	II	INTRAPERITONEAL ONLAY MESH	-	74	140	92	98	02:40:17	02:40:48	31	1	1	2	2	2
91	H	1611711	YD	26	M	68	23.5	I	SEPTOTURBINOPLASTY	-	94	114	70	98	09:45:12	09:45:39	27	0	0	0	0	-
92	H	1619281	S	22	M	72	25.6	I	FUNCTIONAL ENDOSCOPIC SINUS SURGERY	-	84	110	68	98	11:40:45	11:41:14	29	0	1	1	1	-
93	S	1625510	MS	63	M	70	24.2	II	TURBT	-	80	138	84	98	01:15:48	01:16:16	28	0	3	3	4	-
94	S	1615505	MD	27	F	64	23.5	I	HYSTEROLAPROSCOPY	-	90	114	72	98	03:01:15	03:01:41	26	0	5	5	6	-
95	S	1553045	SK	37	M	70	22.1	I	ENDOSCOPIC BIOPSY	-	88	128	74	98	09:45:15	09:45:43	28	1	2	2	2	-
96	S	699288	SK	55	M	101	34.9	II	LAPROSCOPIC CHOLECYSTECTOMY	-	72	118	72	97	11:46:48	11:47:28	40	0	1	4	4	5
97	S	732859	SK	60	F	93	33.1	II	LAPROSCOPIC CHOLECYSTECTOMY	-	68	130	90	98	01:47:10	01:47:47	37	1	2	3	3	4
98	H	1565938	SG	40	F	72	26.4	II	REVISION OF SCAR ON FACE	-	76	140	92	98	03:49:12	03:49:41	29	0	3	3	3	-
99	H	1618148	PK	44	M	94	33.5	II	MICROLARYNGEAL SURGERY	-	68	130	84	97	09:50:15	09:50:53	38	0	0	0	0	-
100	S	1501805	KS	48	M	81	27.2	I	LAPROSCOPIC CHOLECYSTECTOMY	-	80	116	72	98	12:42:41	12:43:13	32	0	0	1	1	1
101	S	1620168	MO	35	F	68	24.9	I	SIALODOCHOTOMY	-	74	124	72	98	03:04:12	03:04:39	27	0	3	4	4	-
102	H	1449343	JS	54	F	73	28.5	II	TYMPANOPLASTY	IBUPROFEN	80	134	84	98	09:51:10	09:51:39	29	0	1	3	3	-
103	S	1614674	MS	29	M	81	25.6	I	INGUINAL HERNIA REPAIR	-	76	110	70	97	11:15:45	11:16:18	33	0	0	1	1	-
104	H	1627208	BB	64	F	53	22.1	II	LAPROSCOPIC CHOLECYSTECTOMY	-	80	140	92	98	01:45:13	01:45:34	21	1	1	2	2	-
105	S	1625994	AB	42	F	67	23.8	II	LAPROSCOPIC CHOLECYSTECTOMY	-	104	110	80	97	03:15:48	03:16:15	27	0	3	3	3	-
106	H	1626122	GS	32	M	88	27.1	II	SEPTOTURBINOPLASTY	-	80	128	84	98	08:51:14	08:51:49	35	0	0	0	1	1
107	H	1626215	NR	51	F	75	28.4	II	TYMPANOPLASTY	-	69	138	84	98	10:48:45	10:49:15	30	1	1	2	2	-
108	S	1628131	BJ	27	M	64	24.2	I	ORIF WITH PLATING	-	98	110	72	98	01:47:42	01:48:08	26	0	4	4	5	-
109	H	1634502	GK	31	F	62	22.7	I	FUNCTIONAL ENDOSCOPIC SINUS SURGERY	-	90	114	70	98	03:48:10	03:48:35	25	0	1	0	-	-
110	S	1064564	HS	33	M	84	29	I	LAPROSCOPIC CHOLECYSTECTOMY	-	70	126	82	98	09:56:03	09:56:36	33	0	3	3	4	-
111	S	1412871	AC	25	M	86	28.8	I	URETEROSCOPY	-	88	116	70	98	11:48:45	11:49:19	34	1	2	4	5	-
112	S	1633978	KK	33	F	58	21.9	I	RECTAL EXAMINATION	-	100	108	72	98	01:56:09	01:56:31	22	0	1	4	4	-
113	S	1535200	RK	32	F	68	24.9	I	FUNCTIONAL ENDOSCOPIC SINUS SURGERY	-	100	114	72	98	03:48:42	03:49:19	37	0	0	4	4	-
114	S	1479858	MK	50	F	86	33.5	II	CYST EXCISION	PENICILLIN	90	140	90	97	09:50:08	09:50:42	34	1	4	4	5	5
115	H	1586375	SS	44	F	61	22.4	II	APPENDICECTOMY	-	92	118	70	98	10:48:05	10:48:30	25	0	0	2	2	-
116	H	101357	CK	45	F	80	29.3	I	STAPLER HAEMORRHOIDECTOMY	-	70	120	82	98	12:16:48	12:17:20	32	0	0	1	0	-
117	S	1024392	SB	40	F	90	33	II	LAPROSCOPIC HERNIA REPAIR	-	80	130	84	98	02:48:05	02:48:41	36	0	2	3	3	3
118	H	700297	AK	54	F	76	29.7	II	PARATHYROIDECTOMY	-	72	118	84	98	09:54:48	09:55:18	30	0	0	0	1	-
119	S	1640529	A	47	F	74	26.3	II	TOTAL LAPROSCOPIC HYSTERECTOMY	-	98	110	68	98	12:10:08	12:10:38	30	1	3	3	4	-
120	H	1635962	R	20	F	62	22.7	I	LAPROSCOPIC OVARIAN CYSTECTOMY	-	74	114	70	99	02:14:48	02:15:13	25	1	1	1	2	-
121	S	840754	KC	32	F	69	29.5	I	LAPROSCOPIC CHOLECYSTECTOMY	AUGMENTIN	76	110	74	99	09:54:47	09:55:15	28	1	2	2	2	-
122	S	1199209	NK	47	F	72	26.4	II	BILATERAL TONSILLECTOMY	-	70	138	90	98	11:48:10	11:48:39	29	0	1	4	4	-
123	H	764213	A	21	M	78	28.6	II	CSF LEAK REPAIR	-	82	126	80	98	02:04:45	02:05:16	31	0	0	0	0	-
124	H	1636854	M	34	F	68	24.9	I	MICROLARYNGEAL SURGERY	-	80	124	86	99	11:05:06	11:05:33	27	1	1	1	0	-
125	S	1631096	S	20	F	60	22	I	CYSTOSCOPY	-	98	108	72	99	01:12:09	01:12:33	24	1	1	2	1	-
126	H	1541256	GS	18	M	74	25.6	I	SEPTORHINOPLASTY	CIPROFLOXACIN,PARACETAMOL	114	110	72	99	03:05:45	03:06:15	30	0	0	0	1	-
127	S	1550081	UD	43	M	82	28.3	II	HERNIOPLASTY	-	88	136	92	98	09:48:05	09:48:38	33	0	0	0	1	-
128	S	1635158	KK	40	F	65	23.8	II	FESS AND SEPTOPLASTY	-	70	128	84	98	11:35:15	11:35:41	26	0	0	5	6	-
129	S	1642813	AK	28	F	65	23.8	I	FUNCTIONAL ENDOSCOPIC SINUS SURGERY	-	80	108	72	98	02:48:02	02:48:28	26	2	5	6	6	-
130	S	1642855	MB	42	M	110	38	II	SOFT TISSUE REPAIR	-	120	114	72	97	09:46:02	09:46:45	43	1	1	3	3	4
131	H	1345180	SK	56	F	78	28.6	II	DIAGNOSTIC LAPROSCOPY & PROCEED	-	68	124	84	97	12:45:57	12:46:28	31	0	2	2	-	-

S.NO.	Randomization	MRD NO	PATIENT INITIALS	AGE (yrs)	GENDER	WEIGHT (kg)	BMI (kg/m2)	ASA	SURGERY PLANNED	DRUG ALLERGY	HEART RATE (/min)	SBP (mm Hg)	DBP (mm Hg)	SPO2 (%)	PROPOFOL START TIME	PROPOFOL FINISH TIME	PROPOFOL ADMINISTRATION DURATION (secs)	PAIN SCORE BEFORE Study Drug	PAIN SCORE FOLLOWING PROPOFOL ADMINISTRATION			
																			AFTER 15 SECS	AFTER 30 SECS	AFTER 45 SECS	AFTER 60 SECS
132	S	647538	JS	52	M	90	31.1	II	TURBT	METRONIDAZOLE	98	128	92	98	02:12:34	02:13:10	36	0	0	5	5	-
133	H	1154961	RK	38	M	86	29.7	II	CYSTOSCOPY	-	70	128	82	98	09:35:48	09:36:22	34	0	0	0	1	-
134	S	1642676	K	38	F	84	30.8	II	TOTAL LAPROSCOPIC HYSTERECTOMY	-	70	138	92	98	11:47:03	11:47:36	33	1	5	6	6	-
135	H	1643736	RS	44	F	58	21.9	II	HYSTERCTOMY	SULFAMETHOXAZOLE+TRIMETHOPRIM	108	108	72	98	12:15:03	12:15:26	23	1	1	2	3	-
136	H	1140417	MK	37	F	68	24.9	I	LIPOMA REMOVAL	-	89	124	72	98	02:15:46	02:16:15	29	0	0	1	-	-
137	H	1643837	RG	31	F	108	38.4	II	HYSTEROLAPROSCOPY	-	110	110	72	97	03:05:40	03:06:23	43	1	1	1	2	1
138	H	1301465	A	23	F	46	18	I	TYMPANOPLASTY	-	118	100	70	99	09:52:03	09:52:21	18	0	0	0	-	-
139	S	1493792	AR	37	F	62	22.7	I	AXILLARY MASS EXCISION	-	90	118	72	98	11:46:20	11:46:45	25	0	2	3	3	-
140	H	1643613	BB	47	M	72	26.4	I	INGUINAL HERNIA REPAIR	-	78	114	72	98	12:16:35	12:17:04	29	0	0	1	1	-
141	H	1642524	JS	43	M	80	27.6	II	FISTULECTOMY	-	70	130	84	98	02:46:25	02:46:57	32	0	1	2	2	-
142	H	1439461	D	30	F	72	27.2	II	RIGHT HEMITHYRIDECTOMY	-	68	140	92	97	09:36:48	09:37:17	29	1	1	2	2	-
143	H	1628133	RG	44	M	72	24.9	I	MICROLARYNGEAL SURGERY	-	74	128	84	98	11:24:46	11:25:15	29	0	0	0	1	-
144	S	1527443	GS	57	M	70	24.2	II	CRANIOPLASTY	-	120	130	90	98	01:15:50	01:16:18	28	0	0	0	1	-
145	H	1590731	VG	47	M	78	28.6	II	TURBT	-	72	140	90	99	03:15:20	03:15:51	31	0	0	0	1	-
146	S	1569434	MK	27	F	80	28.5	II	THYROIDECTOMY	-	94	108	72	99	09:48:10	09:48:42	32	0	4	4	5	-
147	H	1172308	JS	52	M	67	23.8	II	PARAUMBILICAL HERNIA REPAIR	-	74	130	70	99	11:02:40	11:03:07	27	0	0	3	3	-
148	S	1276631	GS	46	M	88	31.3	II	LAPROSCOPIC CHOLECYSTECTOMY	-	74	124	72	98	01:48:50	01:49:25	35	0	3	4	3	-
149	S	1630292	RS	42	M	78	26.9	I	FUNCTIONAL ENDOSCOPIC SINUS SURGERY	-	80	128	72	98	03:05:02	03:05:33	31	0	0	5	5	-
150	H	1608023	GS	28	M	84	27.3	I	FAT GRAFTING	-	94	110	72	99	09:46:50	09:47:24	34	1	1	5	5	-
151	S	1614593	AKJ	60	M	84	29.9	II	LAPROSCOPIC CHOLECYSTECTOMY	-	68	140	92	98	10:05:48	10:06:22	34	0	3	3	4	-
152	S	1629002	JK	55	F	68	25.7	II	RIGHT HEMITHYRIDECTOMY	-	68	132	84	98	01:48:05	01:48:32	27	0	4	5	4	-
153	H	992095	AK	30	F	68	26.6	II	LEFT HEMITHYROIDECTOMY	-	80	132	90	99	03:01:40	03:02:07	27	1	1	1	-	-
154	H	1629404	MB	48	F	64	22.8	II	FUNCTIONAL ENDOSCOPIC SINUS SURGERY	-	80	140	92	99	09:45:10	09:45:35	25	0	0	0	1	-
155	H	1629403	GS	50	M	80	27.6	II	CHOLECYSTECTOMY	-	68	124	72	99	10:45:16	10:45:48	32	0	0	0	1	1
156	H	36373	AK	37	M	61	21.1	II	LAPROSCOPIC CHOLECYSTECTOMY	-	100	110	72	98	02:48:05	02:48:30	25	0	0	0	0	-
157	S	1626272	RM	53	F	84	30.8	II	FUNCTIONAL ENDOSCOPIC SINUS SURGERY	-	72	130	84	97	09:50:45	09:51:18	33	1	2	3	3	4
158	S	1627125	JS	57	M	84	29	II	FESS AND SEPTOTURBINOPLASTY	-	70	140	90	98	11:15:09	11:15:42	33	0	4	4	5	-
159	S	1627907	VK	50	M	90	33	II	RIGHT HEMITHYRIDECTOMY	-	70	130	84	98	12:45:08	12:45:44	36	0	4	5	5	-
160	S	1641788	MT	27	F	58	21.9	I	LAPROSCOPIC CYSTECTOMY	-	88	114	68	99	01:48:35	01:48:58	23	0	2	2	-	-
161	S	1616865	PB	46	F	54	21.1	II	LAPROSCOPIC CHOLECYSTECTOMY	-	74	130	92	99	03:50:25	03:50:47	22	0	0	2	3	3
162	S	1616631	RS	60	M	70	28	II	LAPROSCOPIC CHOLECYSTECTOMY	STREPTOMYCIN,PENICILLIN	68	140	80	98	08:50:45	08:51:13	28	1	1	3	3	-
163	H	1616714	JP	46	M	80	28.5	II	HAEMORRHOIDECTOMY	-	80	140	92	99	09:35:12	09:35:44	32	0	0	1	0	0
164	S	1204234	SK	25	M	65	25.4	II	SEPTAL ABSCESS DRAINAGE	-	82	110	70	96	10:48:30	10:48:56	26	0	2	3	4	4
165	H	1601642	A	23	F	36	18.4	I	TYMPANOPLASTY	-	124	118	64	98	11:15:20	11:15:35	15	0	1	0	-	-
166	H	1459788	J	40	M	70	24.9	II	TOTAL MASTOID EXPLORATION	-	80	128	78	98	02:10:02	02:10:30	28	0	0	0	1	-
167	S	1620760	PS	20	M	78	27.8	II	TONSILLECTEMY & TURBINOPLASTY	-	80	130	84	97	03:10:45	03:11:16	31	0	3	3	4	5
168	H	1314860	RS	48	M	68	23.5	II	ENDOSCOPIC SPHENOPALATINE ARTERY LIGATION	-	80	140	90	98	10:40:20	10:40:47	27	0	0	0	0	-
169	H	1621854	S	28	F	58	23.2	I	FUNCTIONAL ENDOSCOPIC SINUS SURGERY	-	90	114	72	98	11:10:45	11:11:08	23	0	0	0	-	-
170	H	1619980	SK	32	F	74	27.1	I	PAROTIDECTOMY	-	70	128	78	98	01:10:45	01:11:15	30	0	0	0	1	-
171	H	1622378	AS	26	M	72	24.9	I	FESS AND SEPTOPLASTY	-	80	130	84	98	03:02:45	03:03:14	29	0	0	2	2	-
172	S	1552865	AG	32	M	80	26.8	I	VARICOCELE REPAIR	-	74	124	82	99	09:45:12	09:45:44	32	1	3	4	4	-
173	S	485983	SJ	46	F	68	27.4	II	BLADDER REPAIR	-	114	110	72	98	11:40:50	11:41:17	27	1	2	4	4	-
174	S	1625396	HK	40	F	64	23.5	II	HYSTERECTOMY	-	68	134	82	98	12:05:45	12:06:10	25	0	5	5	-	-
175	H	1624579	SB	28	F	64	23.5	II	DIAGNOSTIC LAPROSCOPY & PROCEED	-	92	116	70	98	02:10:12	02:10:38	26	0	0	1	1	-
176	S	1625132	GS	40	M	64	22.8	I	SOFT TISSUE REPAIR	-	88	128	82	98	08:45:12	08:45:38	26	0	4	5	5	-

S.NO.	Randomization	MRD NO	PATIENT INITIALS	AGE (yrs)	GENDER	WEIGHT (kg)	BMI (kg/m2)	ASA	SURGERY PLANNED	DRUG ALLERGY	HEART RATE (/min)	SBP (mm Hg)	DBP (mm Hg)	SPO2 (%)	PROPOFOL START TIME	PROPOFOL FINISH TIME	PROPOFOL ADMINISTRATION DURATION (secs)	PAIN SCORE BEFORE Study Drug	PAIN SCORE FOLLOWING PROPOFOL ADMINISTRATION			
																			AFTER 15 SECS	AFTER 30 SECS	AFTER 45 SECS	AFTER 60 SECS
177	H	1101789	N	28	F	56	21.2	I	HYSTERCTOMY & POLYPECTOMY	-	70	118	80	98	10:45:02	10:45:24	22	0	0	0	0	-
178	H	1616847	KK	55	M	68	24.9	II	TOTAL THYROIDECTOMY	-	74	134	80	98	12:05:24	12:05:51	27	0	0	1	1	-
179	H	1559369	DC	52	M	72	26.4	II	FISTULECTOMY	-	70	138	84	97	02:10:32	02:11:01	29	0	0	0	1	-
180	H	1622337	SSA	30	M	70	24.9	I	TONSILLECTOMY & TURBINOPLASTY	-	80	128	86	98	03:05:15	03:05:43	28	1	1	1	2	-
181	H	1624070	SK	60	F	64	23.5	II	SEPTOTURBINOPLASTY	-	68	134	92	98	09:45:20	09:45:46	26	0	0	0	0	-
182	H	1645316	BB	30	M	74	25.6	I	LAPROSCOPIC CHOLECYSTECTOMY	-	70	118	72	99	11:40:10	11:40:40	30	0	0	0	1	-
183	H	1645246	RK	33	F	72	26.4	II	VENTRAL HERNIA REPAIR	-	98	120	74	97	01:15:20	01:15:49	29	1	1	2	2	-
184	S	1645242	KK	60	F	64	23.5	II	BILATERAL FUNCTIONAL ENDOSCOPIC SINUS SURGERY	-	88	140	78	98	03:01:05	03:01:30	25	0	4	5	-	-
185	S	229920	GS	41	M	84	29	II	LAPROSCOPIC APPENDICECTOMY	-	78	132	74	98	09:40:52	09:41:26	34	0	2	5	5	-
186	S	1645049	SG	62	F	65	24.6	II	EXTENDED TOTALLY EXTRAPERITONEAL REPAIR	-	98	142	74	98	10:05:20	10:05:46	26	0	3	3	4	-
187	S	1645270	SJ	31	M	88	29.5	I	EXAMINATION UNDER ANAESTHESIA	-	78	128	84	99	12:10:45	12:11:20	35	0	2	4	4	-
188	S	1625716	RG	39	F	68	24.2	II	LAPROSCOPIC CHOLECYSTECTOMY	-	89	118	76	99	01:20:30	01:20:57	27	0	4	4	5	-
189	S	1646451	MM	45	F	70	28.2	I	LAPROSCOPIC CHOLECYSTECTOMY	-	88	126	78	98	03:01:45	03:02:13	28	0	4	5	5	-
190	S	1647113	P	39	F	70	29.3	I	LAPROSCOPIC CHOLECYSTECTOMY	-	97	110	78	98	09:55:20	09:55:48	28	0	0	1	1	-
191	H	1645903	AG	35	F	50	24.7	I	LAPROSCOPIC CHOLECYSTECTOMY	-	87	116	78	98	11:05:45	11:06:05	20	0	0	0	-	-
192	S	1305488	AT	18	M	80	23.9	I	SEPTOTURBINOPLASTY	-	96	124	72	99	01:40:06	01:40:38	32	0	1	3	3	4
193	H	1647743	RB	33	F	68	24.2	I	SINUS TRACT EXPLORATION	-	98	110	72	99	03:05:05	03:05:32	27	0	0	0	1	-
194	S	1570226	N	27	F	49	21.1	I	FIBROADENOMA EXCISION	-	91	116	68	99	09:20:12	09:20:32	20	0	0	4	-	-
195	H	1649038	SM	45	F	72	29	II	LAPROSCOPIC CHOLECYSTECTOMY	-	84	100	70	98	11:50:15	11:50:44	29	0	1	1	1	-
196	H	316396	HS	40	M	68	25.7	I	LAPROSCOPIC CHOLECYSTECTOMY	-	91	114	70	99	01:20:45	01:21:12	27	0	0	0	0	-
197	H	1655995	JK	40	F	60	24.2	II	LAPROSCOPIC CHOLECYSTECTOMY	-	80	118	72	96	03:01:20	03:01:44	24	0	0	1	1	-
198	H	1657685	RS	38	F	80	28.5	II	TOTAL LAPROSCOPIC HYSTERECTOMY	-	85	110	64	98	09:50:15	09:50:47	32	0	0	1	1	-
199	S	1656055	RC	24	M	82	28.3	I	PYELOPLASTY	-	69	124	68	99	11:03:05	11:03:37	32	0	1	3	3	-
200	H	1649604	BS	39	M	74	26.3	I	INGUINAL HERNIA REPAIR	-	70	116	72	98	12:02:30	12:03:00	30	0	0	0	0	-
201	H	1593138	JS	46	M	80	27.6	I	SETON WIRE TIGHTENING	-	80	126	78	98	11:50:45	11:51:17	32	0	0	0	1	1
202	S	1644192	SB	32	F	72	25.6	I	LAPROSCOPIC CHOLECYSTECTOMY	-	84	118	78	98	12:05:50	12:06:19	29	1	4	4	5	-
203	S	1644511	RK	50	F	64	23.5	II	LAPROSCOPIC CHOLECYSTECTOMY	-	98	110	74	98	01:45:50	01:46:15	25	0	4	5	5	-
204	H	1492512	A	31	M	70	24.2	II	ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY	-	90	128	70	99	03:01:20	03:01:48	28	0	0	0	1	-
205	H	1598958	RK	44	F	64	23.5	I	HYSTERCTOMY	-	82	114	70	98	09:50:15	09:50:41	26	0	0	0	1	-
206	H	1658952	JD	47	F	69	26.1	II	HYSTERECTOMY	-	68	134	72	99	11:20:30	11:20:58	28	1	1	1	2	-

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The Principal
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Ludhiana

Subject:: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 25.09.2023 has approved the plan of thesis of **Bhawya Chugh**, a student of your college for **MD Anaesthesiology** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis
To evaluate add on effect of hydroxyethyl starch with lignocaine for pain relief following propofol administration.

Supervisor
Dr. Gurpreeti Kaur
Assoc. Prof.,
Dept. of Anaesthesiology

Co-Supervisor:-
Dr. Suneet Kant Kathuria
Prof. & Head
Dept. of Anaesthesiology

The student may submit the thesis in triplicate alongwith the plan in triplicate also, to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She may be directed to attach a photocopy of this letter with the forwarding letter while submitting thesis in the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic, if any.

Controller of Examinations

Note :

1. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*

TO EVALUATE ADD ON EFFECT OF HYDROXYETHYL STARCH WITH LIGNOCAINE FOR PAIN RELIEF FOLLOWING PROPOFOL ADMINISTRATION

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTOR OF MEDICINE

IN

ANAESTHESIOLOGY

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

JULY 2022

DR. BHAWYA CHUGH

DEPARTMENT OF ANAESTHESIOLOGY
DAYANAND MEDICAL COLLEGE & HOSPITAL,
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ABSTRACT OF PLAN OF THESIS

Title	**TO EVALUATE ADD ON EFFECT OF HYDROXYETHYL STARCH WITH LIGNOCAINE FOR PAIN RELIEF FOLLOWING PROPOFOL ADMINISTRATION**
For the degree of	M.D. Anaesthesiology
Name of the candidate	Dr. Bhawya Chugh
Supervisor	Dr. Gurpreeti Kaur, Associate Professor, Department of Anaesthesia, DMCH Ludhiana
Co-supervisor	Dr. Suneet Kant Kathuria, Professor and Head of Department of Anaesthesia, DMCH Ludhiana
Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: Propofol is the most widely used intravenous(i.v) induction agent in anaesthesia. Pain on injection with propofol is a common problem and can be very distressing to the patient. Even with multi-modal techniques, pain on propofol injection is not abolished completely.

HydroxyEthyl Starch (HES), a colloid, is a clinically safe and well tolerated complex polysaccharide and has the capacity to modify endothelial cell junctions and permeability of the vascular endothelium. Pre administration of HES may prevent contact activation by propofol, which may in turn lead to reduced pain during propofol injection.

Aim of Study: To compare the incidence and severity of pain on propofol injection in patients pre administered with 6% HES with 2% lignocaine or 0.9% saline with 2% lignocaine during induction of anaesthesia.

Materials & methods: A prospective randomized study will be conducted on 150 ASA I and II patients of age 18-65yrs undergoing elective surgery under general anaesthesia who will be randomly allocated into group 'H' and group 'N' of 75 patients each. Patients in group 'H' will be administered 50 ml of 6%HES with 2% lignocaine(1mg/kg) while patients in group 'S' will be administered equal volume of 0.9% Saline with 2% lignocaine(1mg/kg) 2minutes before induction with 1%propofol(2mg/kg). The incidence and severity of pain on propofol injection will be calculated using Numerical Pain Rating Scale(NRS) every 15 secs till the loss of verbal command.

Clinical Significance: This study will focus on the efficacy of 6% HES for reduction of incidence and severity of pain after propofol(1%) injection.

Keywords: Propofol, Pain, Hydroxyethyl starch, Lignocaine, 0.9% Saline

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Candidate

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Co-supervisor

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Supervisor

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Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"TO EVALUATE ADD ON EFFECT OF HYDROXYETHYL STARCH WITH LIGNOCAINE FOR PAIN RELIEF FOLLOWING PROPOFOL ADMINISTRATION"** exist in the Department of Anaesthesiology, DMC&H, Ludhiana and will be provided to be candidate. We will see that the data being included in the thesis are genuine and is collected by the candidate herself under our supervision and guidance.

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APPROVAL PROFORMA
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Name of candidate	DR. BHAWYA CHUGH
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PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

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2.	NAME OF THE INSTITUTE	DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA
3.	COURSE OF STUDY AND SUBJECT	M.D. ANAESTHESIOLOGY
4.	DATE OF ADMISSION OF COURSE	07/MARCH/2022
5.	TITLE OF THE TOPIC	TO EVALUATE ADD ON EFFECT OF HYDROXYETHYL STARCH WITH LIGNOCAINE FOR PAIN RELIEF FOLLOWING PROPOFOL ADMINISTRATION

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Propofol is the most widely used intravenous (iv) anaesthetic agent for induction and maintenance of anaesthesia because of its rapid onset and short duration of action and its ease of titration.[1] Despite propofol fulfilling all criteria of being a near ideal anaesthetic, the pain experienced by patient on propofol injection is a deterrent. Some patients recall the induction of anaesthesia as the most painful part of the perioperative period. As a result several interventions have been investigated to alleviate the pain associated with propofol injection.

Pain on injection of propofol can be immediate or delayed.Immediate pain probably results from a direct irritant effect whereas delayed pain which has a latency period of 10 - 20 secs probably results from an indirect effect via the kinin cascade.[2] The cause of pain on propofol injection is not well understood so far, as many factors seem to play a role in causation of pain . These include the site of injection, size of vein, speed of injection, propofol concentration in the aqueous phase and the buffering effect of the blood.[3] Other important factors include the speed of intravenous carrier fluid, the temperature of propofol, syringe material and the concomitant use of drugs such as local anesthetics and opiates.[3] Activation of various nociceptive receptors like 5-HT3 receptors,[4] human transient receptor potential ankyrin 1 (TRPA1][5] as well as irritation of the venular endothelium by the phenol moiety of propofol have also been implicated in propofol injection pain.[6]

According to some studies, vein size is important as they noted that there was no pain when propofol was injected into a larger vein in antecubital fossa. This is presumably because the drug is injected into the midstream of blood flow in the lumen of vein and its contact at high concentration with the sensitive wall will therefore be minimal.[7] Another factor that is important is the duration of exposure of the vein wall to the propofol injection. A slow injection of propofol causes more pain than a rapid

bolus. Perhaps a rapid bolus of the drug is quickly cleared from the vein and is replaced with blood. Pain intensity increases with increased concentration of propofol and at a given concentration is always greater with glucose than with intralipid as the diluent.[8] This is due to reduced concentration of propofol in the aqueous phase. In the Propofol emulsion preparation, the drug will be distributed differently between the two phases,an outer aqueous phase and an inner lipid phase. In a bolus injection, only the outer aqueous phase comes in contact with the intima of the vein. The concentration of an irritating agent in the aqueous phase may be the factor causing venous pain on administration.[9]

Various techniques to mitigate this pain include administration of propofol in a large vein, pre mixing with lignocaine, pre administration of opioids, sub anaesthetic doses of ketamine, using a mixture of medium and long chain triglycerides in the carrier emulsion etc.[6,10,11]

When two or more drugs or measures are used, the incidence of pain of propofol injection decreases considerably. Hence the approach to eliminating Propofol injection induced pain should be multimodal.[12] However, even with multimodal techniques, pain on propofol injection is not abolished completely.

The use of Lignocaine to prevent Propofol injection pain is the most extensively studied technique and is the most common method used in clinical practice. Many studies have shown the use of lignocaine to be effective. Lignocaine can be used as pretreatment before propofol or can be mixed with propofol for reducing pain of propofol injection. The use of lignocaine as a pretreatment to decrease propofol injection pain is based on its presumed local anaesthetic effect on the vein. Lignocaine mixed with propofol decreased its pH, resulting in a lower concentration of propofol in the aqueous phase and therefore reducing pain of propofol injection.[3]

Hydroxyethyl starch (HES) is a colloidal, synthetically modified polymer of amylopectin. It is pharmacologically classified as plasma expander and is

intended to support oncotic pressure and electrolytes.[13] HEShas the capacity to modify endothelial cell junctions and permeability of the vascular endothelium and inhibit endothelial activation by various substances and molecules like Propofol. Its uptake by reticuloendothelial cells may also influence inflammatory responses.[14,15] This modulation of the endothelium by starches has been demonstrated in many in-vivo and in-vitro experimental models. Thus, HES have the capacity to modify endothelial cell junction and may also influence inflammatory responses. Pre-administration of HES may prevent contact activation by propofol, which may in turn lead to reduced pain during propofol injection.

Mistra et al evaluated the effect of 6% HES pre-administration on injection pain using a 3-point Likert Scale following induction with premixed 1%

Propofol and 2% lidocaine. They observed significantly reduced pain on propofol injection which they ascribed to modulation of endothelium by HES administration. Thus we hypothesised that a multimodal technique utilisingcoadministration of 6% HES to 2% Lignocaine will alleviate pain on propofol injection in a more effective manner. Furthermore use of a NRS scale would have higher objectivity in measuring pain intensity. Hence we propose to comparatively evaluate the incidence and severity of propofol injection pain after preadministration of 6% HES with 2% lignocaine versus 2% lignocaine alone in patients undergoing anaesthesia induction with 1% Propofol.

6.2 REVIEW OF LITERATURE

Propofol is the most widely used intravenous anaesthetic agent for induction and maintenance of anaesthesia as well as for sedation inside and outside operation theatre. Propofol has a high incidence of pain on injection when compared to other intravenous anaesthetic agents.[3] As a result several interventions have been investigated to alleviate the pain associated with propofol injection.

Scott et al in 1988 pointed out that certain factors are important in the causation of pain on injection of Propofol. Vein size is important as they noted that there was no pain when Propofol was injected into a large vein in the antecubital fossa. This is presumably because the drug is injected into the midstream of blood flow in the lumen of the vein and its contact at high concentration with the sensitive wall will therefore will be minimal. Morever, drug may also be effectively buffered by blood which it can mix freely. Another important factor is the duration of exposure of the vein wall to the Propofol injection, They noticed that a slow injection of Propofol caused more pain than a rapid bolus. Perhaps a rapid bolus of the drug is quickly cleared from the vein and is replaced with blood. They also observed that there was a species variation in Propofol injection pain. They suggested that pain is likely to be an indirect irritant effect via the release of mediators rather than a direct irritant effect. Furthermore, when the active component of the Propofol emulsion comes into contact with vascular endothelium, it causes release of mediators such as kininogen from the kinin cascade which results in the stimulation of pain. This cause a slightly delayed sensation of pain compared to the immediate sensation of pain that results from a direct effect.[7]

Fischer et al performed a study in 2010 on human and mouse TRPA1 with different formulations of propofol. Their study revealed that transient receptor potential (TRP) channels especially TRP vanilloid 1(TRPV1) and TRP ankyrin 1(TRPA1) which are expressed in peripheral neurons detecting noxious stimuli such as thermal and irritant chemical stimuli are

involved in propofol evoked pain sensation. Stimulation of these channels lead to release of calcitonin gene related neuropeptide from peripheral and central terminals of sensory neurons which induces vascular leakage and dilatation and causes neurogenic inflammation in peripheral and central sensitization in dorsal horn of spinal cord which is the reason of late pain after propofol injection.[16]

A study was done in 2014 by **Nishimoto et al** on mice to know the mechanisms in sensory neurons by which propofol causes pain sensation. They concluded that propofol may cause pain sensation through multiple mechanisms involving not only TRPV1 and TRPA1 but also voltage gated channels downstream of GABA-A receptor activation.[17]

Doenicke et al in 1996 hypothesised that propofol concentration in the aqueous phase may be an important variable for pain associated with propofol injection. In the propofol emulsion preparation, the drug will be distributed differently between the two phases, with an outer aqueous phase and an inner lipid phase. In a bolus injection, only the outer aqueous phase comes into contact with the intima of the vein. The concentration of an irritating agent in the aqueous phase may be the factor causing venous pain on administration.[9]

Eriksson et al in 1997 studied the effects of lignocaine and pH on Propofol induced pain. They came to the conclusion that highest pain rating was observed in the group of the patient that received 1% propofol mixed with saline. The discomfort caused by the injection 1% Propofol mixed with saline was significantly higher than that caused by injection of 1% Propofol mixed either with 1% Lignocaine or hydrochloric acid 0.006 moles/L in the same ratio. The difference in the pain rating between 1% Propofol mixed with 1% Lignocaine and 1% Propofol mixed with hydrochloric acid 0.006moles/L was not significant.[18]

In 1991, **Klement et al** showed that pain intensity increased with the increased concentration of propofol in aqueous phase and at a given concentration, was always greater with glucose than with intralipid as the

diluent. By reducing the propofol concentration in the aqueous phase with intralipid, pain on injection was reduced.[8]

A systematic literature search conducted in 2011 by **Picard et al** for full reports of randomized comparisons of analgesic interventions with placebo to prevent the pain on injection of propofol. They analysed data from 6264 patients(mostly adults) of 56 reports. On average, 70% of the patients reported pain on injection. Fifteen drugs, 12 physical measurements, and combinations were tested. With IV lidocaine 40 mg, given with a tourniquet 30 to 120 s before the injection of propofol, the number of patients needed to be treated (NNT) to prevent pain in one who would have had pain had they received placebo was 1.6. The closest to this camemeperidine 40 mg with tourniquet (NNT 1.9) and metoclopramide 10 mg with tourniquet (NNT 2.2). With lidocaine mixed with propofol, the best NNT was 2.4; with IV alfentanil or fentanyl, it was 3 to 4. IV lidocaine before the injection of propofol was less analgesic. Temperature had no significant effect. The diameter of venous catheters and speed of injection had no impact on pain. From the study, they concluded that for best prevention of pain on injection of propofol, lidocaine 0.5mg/kg should be given with a rubber tourniquet before the propofol injection;of 100 treated patients,approximately 60 have no pain.[19]

Jalota et al in 2015 analysed data from 177 randomised controlled trials totalling 25260 adults and found that overall risk of pain from propofol injection alone was about 60%. They conducted a study to determine the mostefficacious approach for preventing pain on injection of propofol. In their study, they used various drugs like lidocaine-propofol admixture; pre-treatment with lidocaine, various opioids, ketamine, non-steroidal anti-inflammatory drugs; modified propofol formulations containing long chain triglycerides and non drug category incorporating techniques such as site of injection, alteration of temperature of propofol and venous occlusion. They found thatthe two most efficacious interventions to reduce pain on

injection of propofol were use of the antecubital vein, or pretreatment using lidocaine in conjunction with venous occlusion when the hand vein was chosen.[20]

Misra et al in 2022 conducted a study to determine the effect of 6% hydroxyethyl starch pre administration for reduction of pain on propofol injection. The study was done on 126 ASA 1 and 2 patients, 18-65yrs old, of either gender undergoing elective surgeries randomised into two groups. 100ml bolus of HES or 0.9% saline was administered over three to five minutes through an 18G cannula placed in the hand or forearm vein, followed by induction with 1%propofol premixed with 2% lidocaine. They assessed pain during propofol injection every 10 seconds before the loss of verbal command as 0-no pain; 1-mild pain evident only on questioning after 10 seconds without any obvious discomfort; 2-moderate pain self reported by patients within 10 seconds with some discomsfort and 3-severe pain accompanied by withdrawing of hand and behavioural signs. They observed that incidence of pain was significantly higher in the NS group compared to HES group (53% vs 28%). Incidence of severe (8% vs 0%) and moderate pain (16% vs 5%) was higher in the NS group, while the incidence of mild pain was comparable (29% vs 23%; NS vs HES) .A significant difference was seen as wel in the severity of pain between the two groups.Thus, they concluded that pre administration of 100ml bolus of 6% HES 130/0.4 significantly reduced propofol injection pain.[21]

6.3 AIMS AND OBJECTIVES OF THE STUDY

- To compare the incidence of pain on propofol injection in patients receiving HES with Lignocaine versus 0.9% Saline with lignocaine.
- To compare the severity of pain on propofol injection in the two groups.

7. MATERIALS AND METHODS

7.1 SOURCE OF DATA

A randomized study will be conducted in Department of Anaesthesiology of Dayanand Medical College and Hospital, Ludhiana after approval by Institutional Ethics Committee on 206 ASA I and II patients of age 18-65yrs of either gender undergoing elective surgery under general anaesthesia, who will be randomly allocated into two groups of 103 patients each by computer generated randomisation codes contained in sealed, sequentially numbered envelops. A written informed consent will be obtained from each patient.

Patients will be randomized to receive 50 ml bolus of either 6% HES mixed with 2% Lignocaine (1 mg/kg) or 0.9% Saline mixed with 2% Lignocaine before 1% propofol (2 mg/kg) injection. Allocation concealment will be carried out with opaque sealed envelopes which will be opened once the patients are received in the operation theatre.

7.2 METHOD OF COLLECTION OF DATA

Inclusion Criterion

Adults patients of the American Society of Anaesthesiologists(ASA) physical status I and II , 18-65 years old , of either gender and undergoing elective surgery under general anaesthesia.

Exclusion Criterion

- Emergency surgeries or hemodynamically unstable patients
- Patients in whom hand or forearm veins will not be accessible
- Uncontrolled Hypertensives and diabetic patients
- Patients with history of dyspnoea or NYHA III or IV
- Patients with elevated serum creatinine
- Patient refusal
- Known history of allergy to propofol or HES

GROUP ALLOCATION

GROUP H (6%Hydroxyethyl starch with 2% lignocaine)

A total of 103 patients in group H will be given a total bolus of 50ml of 6% HES mixed with 2% Lignocaine(1 mg/kg) over 2 minutes by intravenous route(i.v) before induction with Propofol (1%) injection.

GROUP S (0.9% Saline with lignocaine)

A total of 103 patients in group S will be given a total bolus of 50ml of 0.9% Saline mixed with 2% Lignocaine i.v over 2 minutes before induction with Propofol (1%) injection.

The randomization scheme using computer generated random number will be prepared by our biostatistician and kept in sealed sequentially numbered envelops.

The allocation envelope will be opened by an anaesthesiologist who would not be involved with the direct clinical care of the patient and shall prepare the drugs as per random allocation sequence and hand the sterile study drugs syringes to the anaesthesiologist giving drug to the patient. This anaesthesioloigt administering the drug and the observer recording pain measurements will be unaware of the nature of study drug. These codes would be decoded at the end of study period.

TECHNIQUE

Pre anaesthesia checkup

All patients will be undergoing routine thorough pre anaesthesia checkup one day prior to surgery comprising of detailed history,comorbidities, allergy to any drug especially Propofol, Lignocaine and HES . Physical and systemic examination will be done and relevant investigations will be noted. Patients will be explained that they will receive an IV anaesthetic drug for induction that might cause pain on injection.

To prevent the pain, a drug will be given to the patient according to our study protocol. The patient will be instructed to inform the

anaesthesiologist of the amount of pain they experienced every 15 secs using a Numerical Pain Scale(NRS) from 0-10 with 0-being no pain and 10-most excruciating pain. In addition we shall educate the patient on use of NRS scale. The patient will also be instructed to inform the anaesthesiologist regarding the amount of pain by using fingers of both hands. Written informed consent will be taken from all participants of the study.

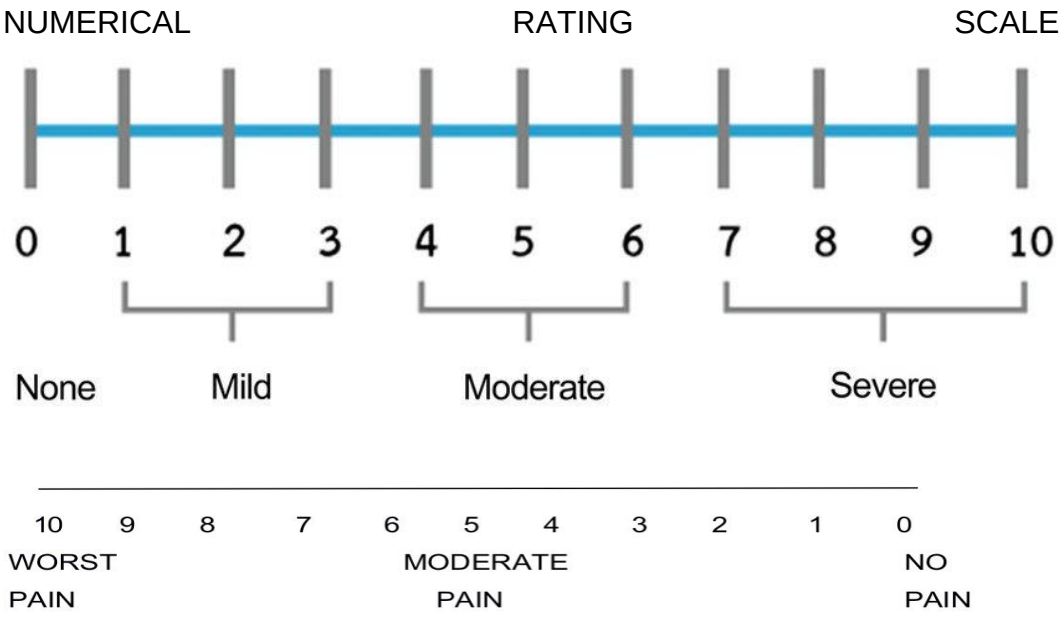
Anaesthesia Technique

In the pre- operative room,after reviewing the investigations and confirmation of fasting and consent, patients will be shifted to the operating room.

On arrival in the operating room, monitors like pulse oximeter, non invasive blood pressure (NIBP), five lead Electrocardiography (ECG) will be attached. And 3 readings of HR, Blood Pressure (BP), SpO2 will be recorded and mean will be calculated and will be considered as baseline reading. An 18G cannula will be inserted either on the dorsum of hand or forearm veins. No premedication will be given to any patient. Patient will be pre-oxygenated with 100% oxygen for 3min.

The study drugs 6% HES (Neon) mixed with 2% Lignocaine(1mg/kg) or 0.9% Saline with 2% Lignocaine (total volume-50ml) will be drawn up in 50 ml syringe (Romson) by an Anaesthesiologist not involved in the study and will be handed over to the Anaesthesiologist who will administer it to the patient over a period of 2 minutes.

After administration of the study drug, 1% Propofol (2 mg/kg) will be administered at the rate of 0.5ml/sec for the induction of anaesthesia. Pain scoring using NRS will be assessed every 15 secs before the patient loses response to verbal commands. NRS scale will be used to determine the severity of the discomfort from 0-10,with 10 being the most severe.After induction and confirmation of mask ventilation, rest of anaesthesia administration will be continued as per standard protocols.



OUTCOME: Following outcomes will be observed:

1. Incidence of pain on propofol injection
2. Severity of pain on propofol injection using NRS.

SAMPLE SIZE CALCULATION

By using previous study (Satyajeet misra et al 22), the Incidence of Pain is 53% in NS group and 28% in HES group

Based on this assumption

The formula used in the situation is as under:

$n = [Z\ 1- \alpha/2 \sqrt{2}\ P\ (1-P) + Z\ 1- \beta\ .\sqrt{\{P1(1-P1) + P2\ (1-P2)\}}]\ 2$

$(P1-P2)\ 2$

Where $P=(P1+P2)/2$

- Approximate value of efficacy/cure rate for standard treatment =P1
- Approximate value of efficacy/cure rate for other treatment = P2
- Effect size = (P2-P1)
- Level of significance (usually 5%)

• Zα = Value of standard normal variate corresponding to α level of significance (1.96)

· Zβ = The standard normal deviate for desired power(0.842)

With the above assumptions the sample size for 95% confidence level & 95% power works out 94 in each study group. To reduce the margin of error, total sample size is taken as 206 (103 subjects in each group).

STATISTICAL ANALYSIS

Data will be described in terms of range; mean ±standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. To determine whether the data is normally distributed, a Kolmogorov-Smirnov test will be used. Comparison of quantitative variables between the study groups will be done using Student t-test and Mann Whitney U test for independent samples for parametric and non-parametric data respectively. For comparing categorical data, Chi square ($\chi 2$) test will be performed and fisher exact test was used when the expected frequency is less than 5. A probability value (p value)less than 0.05 will be considered statistically significant.All statistical calculations will be done using (Statistical Package for the Social Science) SPSS 21version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

The study does not require any investigation or intervention other than those routinely done for every surgery.

7.4 HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Yes, Attached herewith.

8.0 LIST OF REFERENCES

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PROFORMA

MRD No | Patient Initials

Age/Sex | ASA Grade

Diagnosis | Group of patient

Surgery planned | Drug allergy(if any)

BMI | Weight(kg)

Significant history

Comorbidities(if any)

Pre-operative education on use of NRS scale given to the patient-YES/NO

Preoperative assessment

Pain score on the upper limb where study drug will be given-

Vitals-

Time(in minutes)	Heart Rate(per minute)	NIBP(mm Hg)	SPO2
1 min			
2 min			
3 min			

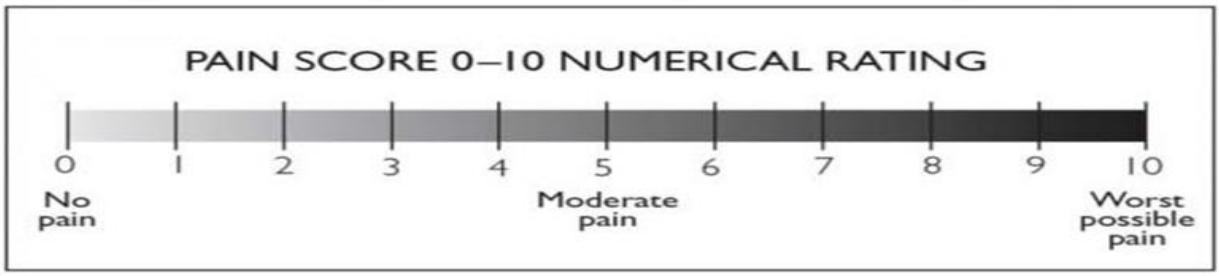
Signature of Candidate **Signature of Supervisor**

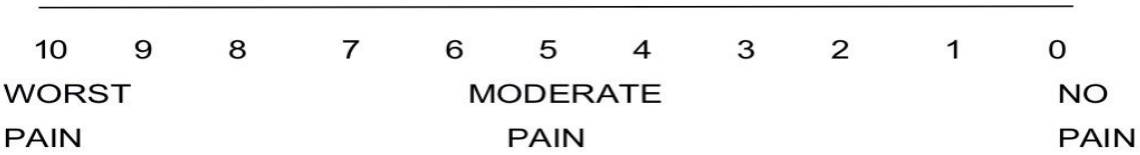
Intraoperative Assessment

(1)Pre-treatment drug time:

(2)Propofol Time: Start Finish

Numerical Pain Rating Scale (NRS)





PAIN ASSESSMENT

Time elapse after start of propofol	15 secs	30secs	45 secs	60 secs
Pain score				

Signature of Candidate **Signature of Supervisor**

INFORMED PATIENT CONSENT

Date: _____

I…….D/o, W/o, S/o……..…… am willing to participate in the study **"TO EVALUATE ADD ON EFFECT OF HYDROXYETHYL STARCH WITH LIGNOCAINE FOR PAIN RELIEF FOLLOWING PROPOFOL ADMINISTRATION"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

……. ……
Signature of the Witness Signature of the patient

Name:

Signature of Candidate **Signature of Supervisor**

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य "**TO EVALUATE ADD ON EFFECT OF HYDROXYETHYL STARCH WITH LIGNOCAINE FOR PAIN RELIEF FOLLOWING PROPOFOL ADMINISTRATION**" में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____	_____
गवाह के हस्ताक्षर	रोगी के हस्ताक्षर/अंगूठे का निशान
नाम:	नाम:

_____

अन्वेषक के हस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

“TO EVALUATE ADD ON EFFECT OF HYDROXYETHYL STARCH WITH LIGNOCAINE FOR PAIN RELIEF FOLLOWING PROPOFOL ADMINISTRATION” ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

_____ _____

ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____ ਮਿਤੀ_____

ਪਤਾ _____ ਪਤਾ _____

_____

ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

_____

ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ